Editorial

JOURNAL OF HEPATOLOGY

Clinical Practice Guidelines of the European Association for the study of the Liver – Advancing methodology but preserving practicability

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The first EASL CPG on treatment of hepatitis C was published in 1999, at that time called a consensus statement. Since then, more than 30 CPGs on various liver diseases have been published. The EASL CPGs are extremely popular in Europe and beyond, making them a global reference for the current state-of-the art on diagnosis and management of liver diseases. As a consequence, the CPGs have been widely distributed, not only by open access publication in the *Journal of Hepatology* and on the EASL website, but also through EASL smartphone apps (*i.e.* iLiver and the HCV Advisor), translations into other languages (*e.g.* Russian and Chinese) and for some CPGs, dissemination of knowledge into derivatives of the CPGs (*e.g.* patient versions).

One possible reason for the success of the EASL CPGs is the streamlined process, which has allowed for a fast response and timely publication of clinical recommendations when there are new developments in a field. This was especially relevant for chronic HCV infection, where the rapid development of treatment regimens has prompted the EASL Governing Board to commission regular updates of "HCV treatment recommendations" on an almost yearly basis since 2014. For hepatitis B, the first CPG was launched in 2009, followed by updated versions in 2012 and 2017. This responsive process of CPG development in almost all areas of hepatology has only been made possible by the commitment of a small team of 5–8 world-leading experts (the "CPG panel") and the meticulous evaluation of the CPGs by three independent experts (at least one from outside Europe), as well as the EASL Governing Board. EASL is very grateful for the continuous and outstanding support provided by these experts from our community.

However, the current process of EASL CPG development also has limitations. With CPGs on several different topics for which quite different types of scientific evidence (both quantitative and qualitative) could be consulted, the format and methodology of the CPGs has become heterogeneous with time. As an example, several CPGs have used different methods for grading the evidence. Sometimes the methods for assessing the level of evidence and reaching a recommendation have not been clearly disclosed, and international standards for CPG development have not been fully adopted.[1] Moreover, due to the small panel, the involvement of the broader academic community as well as of other stakeholders (*e.g.* patients and other specialist groups) has been limited. In addition, the use of a small, yet efficient panel inherently poses the risk of introducing unintentional bias into the recommendations, especially for controversial topics where evidence may be conflicting and expert consensus may not exist.

These considerations prompted the EASL Governing Board to revise the process for EASL CPGs and Treatment Recommendations. This revised process, which is currently being implemented, aims to more stringently harmonise methodology and presentation of different CPGs, to be more transparent in the generation of the recommendation statements and finally to allow for input from the broader EASL community (Fig. 1). Ideally, improvements would minimally affect the major strength of the current CPGs, which is practical utility and timeliness.

An important component of the revised process is the inclusion of a simplified Delphi process to reach a broader consensus and involve academic experts and other stakeholders beyond the CPG panel and the EASL Governing Board. A Delphi process is an iterative way of obtaining a collective view from individuals about relevant issues, especially where there is scarce or conflicting evidence and reaching a final opinion is important. In the CPG procedure, the Delphi process will be questionnaire-based and provides two rounds of feedback to the CPG panel. This design will avoid group dynamics and risk of bias, and allow panellists to reassess their views in the light of the responses of the consulted group as a whole.

In order to account for the considerable differences of available scientific evidence in the various areas of hepatology, EASL will refer to two different formats of practice recommendations, which will be EASL Clinical Practice Guidelines and EASL Position Statements.

Received 18 October 2018; accepted 18 October 2018

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† The European Association for the Study of the Liver (EASL) regularly publishes Clinical Practice Guidelines (CPGs) and Treatment Recommendations (http://www.easl.eu/research/our-contributions/clinical-practice-guidelines). These documents aim to help clinicians to optimise their management of patients with liver diseases, based on the most current scientific evidence and, where evidence is scarce, consensus opinion of experts from the field.

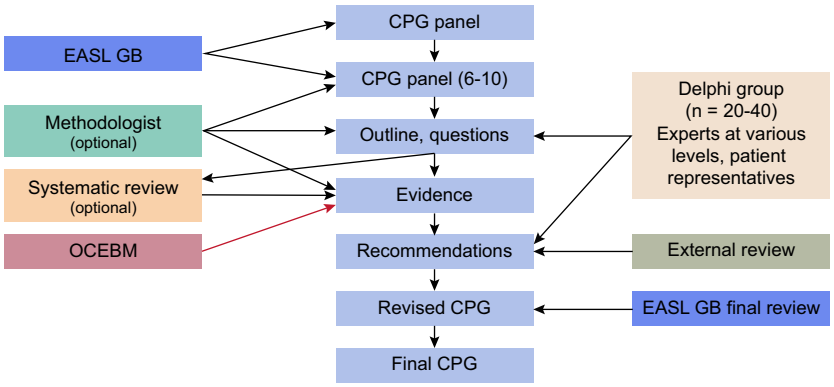

Fig. 1. New process for development of the European Association for the Study of the Liver Clinical Practice Guidelines. CPGs, Clinical Practice Guidelines; EASL, European Association for the Study of the Liver; GB; Governing Board. OCEBM, Oxford Centre for Evidence-Based Medicine.

Table 1. Key components of high-quality and trustworthy guidelines on clinical practice according to the guidelines interactional network.[1]

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

Table 2. Example of a question using the P.I.C.O. structure.

P	**P**atient, **P**opulation, or **P**roblem
I	**I**ntervention, Prognostic Factor, or Exposure
C	**C**omparison or Intervention (if appropriate)
O	**O**utcome you would like to measure or achieve
Example	Should patients with primary sclerosing cholangitis be treated with ursodeoxycholic acid to prevent or decrease liver related complications? **P** = Patients with primary sclerosing cholangitis **I** = Treatment with ursodeoxycholic acid **C** = No treatment **O** = Liver related complications

Details available: https://www.cebm.net/2014/06/asking-focused-questions/[2].

EASL Clinical Practice Guidelines should give practical guidance on relevant topics in liver diseases and should follow a standardised method that complies with the international standards for CPGs according to the guidelines international network (Table 1).[1] The CPGs will be regularly updated after a defined expiration date or as an exception before the expiration date, if deemed necessary by the EASL Governing Board. The EASL Governing Board decides on the topic and determines the chair of the panel, and the Governing Board and the panel chair jointly select the panel, which consist of 5–8 experts in the field, including one Governing Board representative. The EASL Ethics Committee must approve any financial conflicts of interest declared by the panel chair and members prior to acceptance to the panel.

The process is initiated by the panel drafting and approving 5–25 clinically relevant questions considering the patient-intervention-comparison-outcome (PICO) format (Table 2).[2] The PICO format is a standardised method to address the patient population, the intervention, comparisons and the outcome. This approach will harmonise the outline of the CPGs and ensure that the most relevant questions related to the topic of the CPG are addressed. The panel will draft recommendations based on the evidence, which will be rated based on the Oxford Centre for Evidence-Based Medicine (OCEBM) (Table 3).[3] OCEBM is an evidence ranking system designed to find the likely best evidence regarding a specific question. In contrast to GRADE it can be used even if there are no systematic reviews available.

The panellists are responsible for making an unbiased selection of literature to determine the level of evidence for their recommendations. A systematic review or meta-analysis of the literature base is not mandatory, but may be performed or commissioned by the CPG panel for subtopics and particular

Table 3. Level of evidence based on the Oxford Centre for Evidence-based Medicine (adapted from The Oxford 2011 Levels of Evidence[3]).

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of Randomized controlled trials (RCT)	*Further research is unlikely to change our confidence in the estimate of benefit and risk*
2	Randomized controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (i.e. non-randomized, retrospective)	
3	Non-randomized controlled cohort/follow-up Study/control arm of randomized trial (systematic review is generally better than an individual study)	*Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate*
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (Mechanism-based Reasoning)	*Any estimate of effect is uncertain*

*Level may be graded down on the basis of study quality, imprecision, indirectness (study does not match questions), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

Table 4. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested may not, is not suggested	

questions in need of deep assessments. This compromise, to not make a systematic review mandatory, allows for a relatively fast process of CPG development, a strength of the previous CPGs, whilst at the same time providing the opportunity for deeper analysis of controversial topics. Besides the evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations and feasibility are also considered for the grade of recommendation (Table 4).

The Delphi process will be implemented at two points throughout the CPG development process. The outline of the PICO questions and later the draft recommendation statements will be reviewed by an international panel of 20–40 experts, including at least one patient representative. The panel and the EASL Governing Board jointly nominate the group to be consulted by the Delphi process. At the time of launching, the technical solution will be supported by the Clinical Guideline Service group (https://www.guideline-services.com), which provides an online platform, where all CPG documents are uploaded and reviewed.

EASL Position Statements will follow a similar methodology as the CPGs. However, for position statements the PICO step and Delphi process are not mandatory. The position statement should address an emerging topic that demands a very fast process, and holds similarities with the existing EASL CPGs. There is no expiration date, but usually a CPG should ultimately follow on the topic in due time.

Both CPGs and position statements will be peer-reviewed by international experts (at least one from outside Europe) and finally by members of the EASL Scientific Committee, prior to approval of the final manuscript by the EASL Governing Board.

With the implementation of the revised CPG and the new position statement processes EASL aims to harmonise the documents produced by the association, to be transparent on the methods and still ensure rapid production and practical utility. We are confident that the previous EASL recommendations, given by top-level experts in the field and rigorously reviewed by independent referees, were evidence-based, rational and important for our patients. However, the current improvements still represent a necessary step towards avoiding methodological inconsistencies in a medical field of increasing regulation and scrutiny. As such, the revised process, where significant methodological stringency is accompanied by perspectives of practical implementation and experience, the patient voice included, seem to provide the right blend of various types of input to best practice. At least, the modifications to the EASL CPG process will further improve the scientific rigor of the recommendations. In our view, the new EASL CPG process is the most reasonable, scientifically accurate, transparent and at the same time pragmatic method to develop practical recommendations that will help anyone who is involved in liver diseases optimise the management of their patients.

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Author names in bold designate shared co-first authorship

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