Guidelines Office Systematic Review Handbook

Version July 2025





INTRODUCTION

The European Association of Urology (EAU) Guidelines Systematic Reviews Methods and Processes Handbook provides guidance to the EAU Guidelines Panel Members and Associates for the preparation of systematic reviews (SRs) under the auspices of the EAU Guidelines Office.

We have divided the Handbook into different sections which correspond to the main steps to be followed in the production of a Systematic Review. An Appendix Folder which describes the most important Templates is provided at the end of this Handbook.

We also refer to the following paper: "Key Steps in Conducting Systematic Reviews for Underpinning Clinical Practice Guidelines: Methodology of the European Association of Urology" [1].

The previous version of the Handbook dates from 2019. The Handbook is updated regularly to reflect advances in systematic review methodology and in response to feedback from EAU Guideline Panels.

AUTHORS

EAU Guidelines Methods Committee

Prof. Dr. Steven Canfield (chair) Dr. Imran Omar (vice-chair) Dr. Steven MacLennan Dr. Lorenzo Marconi Prof. Catrin Tudur Smith Dr. Cathy Yuhong Yuan Dr. Arjun Nambiar Dr. Bhavan Rai Dr. Vasileios Sakalis Prof. Dr. Maria J. Ribal (ex-officio)

STEP 1: FORMULATION OF THE SYSTEMATIC REVIEW QUESTION

1.1 Selection of the review topic

- The systematic review (SR) question is selected and prioritised during the Panel's meeting (by panel consensus). Ideally, a draft of the SR Request Form (please see Appendix folder Templates 1 4), including the PICO elements, is done at the same meeting. The criteria for prioritisation of a new SR should be:
 - Impact of the health problem (measured by disease incidence, financial cost, morbidity and mortality);
 - Potential to change a guideline recommendation;
 - \circ $\;$ Availability of a body of evidence that could potentially answer the research question;
 - Absence of published, updated and high-quality systematic reviews concerning the same research question (please see 1.2)
 - When a guidelines recommendation lacks a supporting systematic review
- An initial literature search performed by the Panel Associates should be done at this stage to ensure there is sufficient data to warrant a review; and also, to check if similar reviews on the same topic have been previously published. PROSPERO should be checked for ongoing reviews. If any are identified, the review team should be contacted to know its status and explore the possibility of collaboration.

1.2 Assessment of similar reviews already published

If the group identifies an already existing up to date SR, its appropriateness and quality should be assessed before deciding to use that review to answer the research question. For that purpose, the 3 following criteria must be met:

- 1. **Overall Confidence Criteria**: the review should be of high methodological quality using the AMSTAR 2 tool [2] this is defined by fulfilling at least ONE of the following two criteria:
 - Scoring positively for at least 10/16 and at least 6 of the following 7 critical domains: Protocol registered before commencement of the review (item 2); Adequacy of the literature search (item 4); Justification for excluding individual studies (item 7); Risk of bias from individual studies being included in the review (item 9); Appropriateness of meta-analytical methods *if applicable* (item 11); Consideration of risk of bias when interpreting the results of the review (item 13); Assessment of presence and likely impact of publication bias (item 15); OR
 - Scoring positively for all 7 essential domains.
 - The Methods Committee recognises that the above mentioned 7 critical items will not always be regarded as critical and appraisers may add or substitute other critical domains if applicable, with the supervision of the methods committee [2].
- 2. **Similarity Criteria**: A complete overlap of the objectives, PICO elements and search strategy should be ensured (please see 1.3).
- 3. **Up to date Criteria**: The literature searches in the published Systematic Review should be no more than 2 years old. Older searches may be accepted provided there is no new evidence identified by scope searches within the panel.

Three possible outcomes of the assessment are:

a) If the SR fulfills the Overall Confidence criteria, addresses the PICO of interest and is up to date, its findings can be used to directly inform the panel's recommendations.

- b) If the SR fulfills the above criteria, addresses the PICO of interest but is out of date, the panel should consider doing a new systematic review. To update the review and include any newly available information, a further de novo systematic review can be carried out to identify new PICO-related literature published after the final search date of the available evidence summary. For the incorporation of new studies into an existing SR, the panel should assess the new studies as a new SR on just these new studies (or least assess the new studies using the methodology used in the previous SR report or publication), add these new studies to the previous SR, and then write a new SR report (and eventually prepare a new SR publication) which includes the new studies to document what has been done and the results. The combined evidence will then be used by the panel to formulate its recommendations
- c) If the existing SR does not meet the Overall Confidence Criteria described above or does not overlap with the question being addressed by the panel, then the evidence summary should not be used by the panel and the panel should propose a new SR.

1.3 Initial processes and submission of the systematic review request form

After the research question is defined, the panel should establish the lead Panel Member responsible for the review, the lead Associate Member and a second Associate Member. (In case there is a need for new associates, it should be stated in the SR Request Form.) In some guideline panels, a **methodology lead** within the panel may be designated to oversee the methodological aspect of the systematic review development process. This role, when present, complements the **lead panel member** and the associate responsible for developing the systematic review.

- The PICO elements should be further developed by the Associate and the lead panel member / panel chair. The process of PICO development can be found elsewhere [1]. Whenever possible, the selection of the Outcomes (O) should be based on agreed standardized sets of outcomes (Core Outcome Sets - COS) for a specific condition. COS for specific conditions can be searched on specific databases such as the COMET database (http://www.cometinitiative.org) or ICHOM (https://www.ichom.org).
- The associates will fill out a first draft of the SR/Literature Search Request Form containing the PICO elements. There are separate forms for Interventions, Prognostic Factors and Diagnostic Test Accuracy reviews. The most up to date versions of the forms are stored in Dropbox. (UROWEB DROPBOX → 5. Documents for the associates → 1. Templates) or (Appendix folder Templates 1 3)
- Upon their review and approval, the Associates should circulate this form to the panel members for approval. The form should be signed off by the Lead Panel Member and by the Panel Chair.
- After approval of the SR/Literature Search Request form by the panel, the Associates should submit it for final approval to the Methods Committee. The Guidelines Office Staff Member who works with the Panel should send the Request Form to the Methods Committee via email.
- The Methods Committee will review the form and send their comments and eventual decision back to the Senior Associate (cc Panel Chair, Responsible panel member, Associates) in 10 working days.
- After final approval of the SR Request Form by the Methods Committee, the associates should start developing the Search Strategy and the Systematic Review Protocol (please see Step 2)

1.4 Structure of the systematic review shared online folder

• After approval by the Methods Committee, a Systematic Review (SR) shared online Folder is then created by the Guidelines Office Staff Member who works with the Panel and shared

with: Panel Chair, Responsible Panel Member, , Associates and Methods Committee.

• Each SR FOLDER should be coded in the following manner: Year-Panel Initials-KEY WORDS OF REVIEW (e.g. 2024-RCC-Systemic Treatment)





STEP 2: SEARCH STRATEGY & DEVELOPMENT OF THE REVIEW PROTOCOL

2.1 Development of the review protocol

- The protocol is prepared by the Associates using one of the mandatory EAU SR Protocol Templates (Appendix Folder Templates 4-6)
 - Intervention SR Protocol (Template 4)
 - Diagnostic Test Accuracy SR Protocol (Template 5)
 - Prognostic Factor SR Protocol (Template 6)
- The protocol should be sent by the lead associate for comments and approval to the following SR members: Panel Chair and Lead Panel Member, Information Scientist. The Protocol should be signed off by the Lead Panel Member and by the Panel Chair.
- The SR Protocol should then be submitted by the lead Associate to the Methods Committee for first review. The Protocol is sent via email to the Methods Committee by the GO Staff Member working with the Panel. All comments by the methods committee and the responses to these comments should be made using Track Changes in Word.
- After Final Review, the methods committee makes a final decision to proceed or not with the Systematic Review under the auspices of the EAU Guidelines.
- The submission to PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) should be done by the lead Associate before the completion of data extraction.

2.2 Search strategy

- The lead Associate sends the approved PICO elements/literature search request form to the Information Scientist.
- The search strategy may need to be further tailored by the review team (lead Associate, lead Panel Member) and the Information Scientist.

• Once the Information Scientist retrieves the list of references, the Associate is responsible for uploading the abstracts identified by the literature search in the SR FOLDER defined above.



Figure 2: Initial process for Methods Committee (MC) approval

STEP 3: SCREENING AND SELECTION THE STUDIES FOR REVIEW

3.1 Abstract screening

- All abstracts should be independently screened by 2 associates (double screening) to determine if they are potentially eligible for inclusion in the SR and the full text obtained for further review.
- The lead panel member will act as an arbitrator if a disagreement occurs. Furthermore, they are responsible for screening the first 100 abstracts with the associates and then a 2% random check of the remaining abstracts to be screened.
- The Excel Abstract Screening Form should be filled by the 2 associates (available in the SR FOLDER)

		Reviewer 1		Reviewer 2		AGREEMENT		
Abstract_n r	Decision	Remarks	Decision	Remarks	Final Decision	Remarks	KEY	
1								0 Excluded
2								1 Included
3								2 Unclear
4								
5								
5								
,								
3								
)								
10								
11								
12								_
13								_
14								_
15	1		1					

Figure 3: Abstract Screening Form

(Other programs such as Endnote can eventually be used for the abstract screening; Systematic Review specific software may be used to conduct various steps of a systematic review.)

Manual: "Using EndNote for Abstract Screening" (UROWEB DROPBOX \rightarrow 5. Documents for the associates)

3.2 Full-text screening and selection of studies

- The full-texts should be retrieved by the Associates. In order to minimize expenses, the bibliographic resources of the institutions of the involved associates should be used. If the full-text is not available at their institution, the Guidelines Office Staff working with the panel should be contacted for full-text retrieval.
- PDF files of the full-texts should be stored in the appropriate subfolder of the online SR FOLDER. The names of the PDFs should use the following ID: Author, Journal Abbreviation, Year, Page Range, First four words of Title.

- All the full texts should be independently screened by 2 Associates.
- The Lead Panel Member will act as an arbitrator if a disagreement occurs.
- The Excel Full-text Screening Form should be filled out by the associates (available in the appropriate subfolder in the SR Folder

Figure 4: Full Text Screening Form

FULL-TEXT SCREENING (Systematic Review ID)																			
						Reviewer 1		Reviewer 2 AGREEMENT					SREEMENT						
Abstract nr	Study ID	PI	С	0	Decision	Reason for exclusion (codified)	Remarks	Ρ	I.	с	0	Decisi	on	Reason for exclusion (codified)	Remarks	Final Decision	Remarks	KEY	
																		Q	Excluded
																		1	Included
						1												2	Unclear
																		Y	YES
																		N	No
								1										1	

3.3 Policy for non-English papers

Most SR exclude non-English language papers; however, in case there are no language exclusions abstracts should be translated when feasible into English by the associates if an English language version is not available. Relevant Guideline Office staff can be contacted for their advice if non-English language is not covered by the review team and the panel. Then, based on the abstract:

- All RCTs should be translated (Methods and Results section).
- Large prospective comparative non-randomized studies should only be translated if evidence from RCTs is lacking.
- Translation of retrospective studies and other designs needs the approval of the methods committee on a case-by-case basis.

STEP 4: DATA EXTRACTION FOR ANALYSIS AND APPRAISAL OF THE RISK OF BIAS

4.1 Data Extraction

- The Data Extraction Form (DEF) should be prepared by the Associates under the supervision of the Methodology lead (if available) and be sent for comments to the Lead Panel Member.
- We recommend using an Excel DEF with a separate row for each study. An example can be found at UROWEB DROPBOX \rightarrow 5. Documents for the associates \rightarrow 1. Templates.
- OUTCOME DATA extraction should be done independently by two Associates for a minimum of 10 papers and a maximum of 20 (if the discrepancies are minimal, the rest can be data extracted by 1 then checked by the 2nd). The data extraction for non-outcome data is done by the lead associate only.

4.2: Appraisal of the risk of bias (RoB)

4.2.1 RoB Tools for systematic reviews of Comparative Effectiveness of Interventions

In systematic reviews of Comparative Effectiveness of Interventions, the following RoB Tools should be used:

- Randomised Controlled Trials (RCTs): Cochrane Risk of Bias Tool (2008) or Cochrane Risk of Bias Tool 2 (Please refer to the Cochrane Handbook and to the next section for more information) [3].
- Non-Randomised Comparative Studies (NRCS): ROBINS- I tool. (please cite: terne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. <u>ROBINS-I: a tool for assessing risk of bias in nonrandomized studies of interventions</u>. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919.)
- Case Series: The 5-criterion Quality Appraisal Checklist

- The EAU GO needs to make recommendations using available evidence. Sometimes, case-series studies are the only source of research evidence available to inform decisions. Furthermore, some important outcomes may not be reported in RCTs or NRCS. For example, rare adverse events may be easier to ascertain in Case Series where larger sample sizes and longer follow up may be available. Because case-series studies are prone to various types of biases in relation to selection, performance, detection, attrition, and reporting, the derived results are generally ranked as low quality.
- For assessing the methodologic quality of case-series studies. We suggest the use of a 5-criterion quality appraisal checklist.
 - 1. Was there an a priori protocol?
 - 2. Was the total population included or were study participants selected consecutively?
 - 3. Was outcome data complete for all participants and any missing data adequately explained/unlikely to be related to the outcome?
 - 4. Were all prespecified outcomes of interest and expected outcomes reported?
 - 5. Were primary benefit and harm outcomes appropriately measured?

Answer yes/no to 5 questions:

- > If all 'yes', the study is at 'low' risk of bias.
- > If any are 'no', the study is at 'high' risk of bias

4.2.2 RoB Tool for Systematic reviews of Diagnostic Test Performance Studies

In Systematic reviews of Diagnostic Test Performance, QUADAS-2 should be used. [4]

- QUADAS-2 (http://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/) is the tool that we recommend for use in systematic reviews to evaluate the risk of bias and applicability of primary diagnostic accuracy studies. QUADAS-2, consists of four key domains:
 - o patient selection
 - $\circ \quad \text{index test} \\$
 - $\circ \quad \text{reference standard} \quad$
 - $\circ \quad \text{flow and timing} \quad$
- Each is assessed in terms of risk of bias and the first three in terms of concerns regarding applicability. Signalling questions are included to assist in judgements about risk of bias.

4.2.3 RoB Tool for Systematic reviews of Prognostic Factors

In Systematic Reviews of Prognostic Factors, the QUIPS tool should be used.

- The QUIPS tool [5] is the recommended tool for the assessment of RoB of Prognostic Factor Studies. It has 6 bias domains:
 - 1. Study Participation
 - 2. Study Attrition
 - 3. Prognostic Factor Measurement
 - 4. Outcome Measurement
 - 5. Study Confounding
 - 6. Statistical Analysis and Reporting
- For each of the 6 domains in the QUIPS tool, responses to the prompting items are taken together to inform the judgment of risk of bias. Information and methodological comments supporting the item assessment should be recorded (cited directly from the study publication). Judgments should be made with consensus among at least 2 assessors. Some items may not be relevant to the specific study or the review question and may be skipped or omitted.
- Each of the 6 potential bias domains is rated as having high, moderate, or low risk of bias.

• To judge overall risk, one could describe studies with a low risk of bias as those in which all, or the most important (as determined a priori), of the 6 important bias domains are rated as having low risk of bias.

4.2.4 Presentation of Risk of Bias Summaries

- For consistency of presentation, when possible bias summary graphs should be created using the RevMan or other software. The principles underpinning the various risk of bias tools previously described should be applied. This can be manipulated to show the desired domains whilst indicating 'high' (red circle, '-' symbol), 'low' (green circle and '+'symbol) or 'unclear' (yellow circle and '?' symbol) risk of bias.
- The presentation of the bias domains in graphs in the systematic review report should be as follows:
 - For systematic reviews only including randomized controlled trials (RCTs), display all the domains from the Cochrane risk of bias tool.
 - For performance bias (i.e. blinding of participant and personnel) presentation should be limited to one domain.
 - $\circ~$ For detection bias (e.g. blinding of outcome assessment) presentation should be limited to 2 domains:
 - Patient reported outcomes, for e.g. function questionnaires or pain scores (i.e. blinding of participants). If no patient reported outcomes are included in the review, then only one detection bias domain needs to be reported.
 - Clinician reported outcomes, for e.g. death, recurrence etc. (i.e. blinding of personnel)
- For reviews only including non-randomised comparative studies (NRCS), display all the domains from Robins I tool (Confounding; Selection; Classification of Interventions; Deviations from interventions; Missing data; Measurement of Outcomes; Selection of the reported result and Overall Bias.
- For reviews only including single-arm studies, they should report all the domains outlined in the tool described in the protocol template including 'outcome measurement bias'
- Outcome measurement bias should be limited to the 2 most important outcomes, usually the primary harm and primary benefit outcomes.
- For reviews including RCTs and NRCS, separate graphs should be used to present the RCT bias domains and the NRCS bias domains. For RCTs, do not modify the Cochrane tool (e.g. do not display confounder scores).
- For reviews including RCTS, NRCS and single arm studies, the risk of bias assessment should be presented in 3 separate graphs.

STEP 5: SYNTHESIS OF THE FINDINGS/OVERALL QUALITY OF EVIDENCE ASSESSMENT

- Summary of Baseline Characteristics and Results tables should be produced and sent to all panel members at least 1 week before the meeting to allow a fruitful discussion. Associates should use the Results section of the Systematic Review Report Template to present the results (please see STEP 6.1, Systematic Review Report)
- Meta-analysis is the statistical combination of results from two or more separate RCTs. Potential advantages of meta-analyses include an increase in power, an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. However, they also have the potential to seriously mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered. It is not considered appropriate to combine non-randomized trials in a meta-analysis. However, if

the outcomes reported in NRCS are sufficiently similarly defined, it may be appropriate and feasible to display the results of these studies in a forest plot, omitting a pooled estimate of effect. (Figure 5) Advice should be sought from the methods lead and if required also the methods committee before proceeding.



Figure 5: Forest Plot omitting a pooled estimate of effect [6]

STEP 6: PRODUCTION OF A FINAL SR REPORT and MANUSCRIPT FOR PUBLICATION

6.1 The systematic review report

- A SR Report should be prepared using the SR Report template. There are 3 available SR Report templates (UROWEB DROPBOX → 5. Documents for the associates → 1. Templates)
 - Intervention SR Report Template (Template 7)
 - Diagnostic Test Accuracy SR Report Template
 - Prognostic Factor SR Report Template
- In order to incorporate SR findings into the Guideline, the SR report should be prepared and presented to the panel.
- The systematic review report represents a basis for the SR Manuscript (see 7.2)
- After finalisation, the SR Report can be published online (uroweb).

6.2 The systematic review report

- The Lead Associate should prepare the first draft of the SR Manuscript for publication in a pre-selected peer reviewed journal and send it to the lead panel member.
- After the contribution of the responsible Panel Member, the paper should be circulated to all co-authors for their comments and approval.
- The finalised paper is submitted to the peer-reviewed journal
- Once the paper is accepted for publication, the senior or associate who submitted the protocol to PROSPERO should access the record and update it, including a link to the publication.

6.3 Authorship rules – Associates and senior associates

- Authorship roles should be clarified at the outset in accordance with the EAU authorship policy. (UROWEB DROPBOX \rightarrow 5. Documents for the associates)
- Will be acknowledged in the main guideline document as co-authors
- Are expected to be co-authors in the shortened guideline document for publication in European Urology
- Are expected to be co-authors in the systematic review paper for publication in a peerreviewed journal. The lead associate is usually the first author and the second reviewer usually the second author. However, if the progress of the lead associate/s is not

satisfactory, then someone else may take lead, and if that happens then the order of authorship will be changed to reflect their contribution.

STATUS OF THE REVIEW PROCESS

A record of the dates of start and completion of the main phases of the review should be recorded by senior associates in the AUDIT DOCUMENT (found in each SR FOLDER).

SR ID: Year-Panel Initials-key word		GUIDELINES INCLUSION YEAR:			
STEP	DATE STARTED	DATE COMPLETED			
SR Request Form delivery					
Methods committee approval of the Request Form					
Protocol development					
Methods committee approval of the Protocol					
Search strategy					
Abstract screening					
Full-text screening					
Data extraction / IPD request					
Statistical analysis					
SR Report					
Presentation of SR Report to the Panel					
Manuscript Preparation					
Publication Submission					

ROLES OF TEAM MEMBERS INVOLVED IN THE SYSTEMATIC REVIEW

- Expectations and responsibilities of panels and panel members involved in review
 - To devise PICOs
 - Panel Chair to sign off the SR/Literature Search Request form and the SR Protocol for Methodology Committee approval
 - To oversee all clinical aspects of the systematic review
 - To provide support to the associates involved in the review
 - To assist in clinical queries and to respond in a timely manner

0

- Expectations and responsibilities of methodologists
 - To advise on methodological issues and to respond to methodological queries in a timely manner
 - Reviewing the data extraction form, carrying out the meta-analysis, IPD analyses
- Expectations and responsibilities of panel member(s) acting as Methodology lead
 - To support associates in review work: providing methodological and clinical guidance and acting as arbitrator
 - To submit the SR/Literature Search Request form and the SR Protocol for Methodology Committee approval with the assistance of the GO Staff Member working with the panel
 - Submit SR protocol to PROSPERO

- \circ $\:$ Upload the list of references provided by the Information Scientist in the Dropbox SR $\:$ FOLDER
- Screening the first 100 abstracts with the associates
- 2% random check of the abstract screening
- Liaise with panel members to provide progress reports or seek clinical guidance
- $\circ \quad \text{Liaise with methodologist regarding methodological issues}$
- Together with panel leads, deliver results to review panel
- \circ $\$ Record of the dates of start and completion of the main phases of the review
- Expectations and responsibilities of associates
 - Attend workshop trainings and panel meetings when invited
 - Undertake all aspects of review work
 - Prepare the SR/Literature Search Request form
 - > Write protocol
 - Prepare data extraction forms
 - Perform abstract and full text screening
 - Liaise with senior associate and panel members regarding progress or problems
 - Prepare baseline characteristics and summary of results tables within agreed timelines
 - Participate in additional activities as may be requested under the auspices of the EAU Guidelines Office (e.g. SCOPE searches, Core Outcome Sets, Consensus Projects, grant and projects e.g. PIONEER and OPTIMA)
- Expectations and responsibilities of information scientists
 - To liaise with the Associate(s) and panel members to clarify search terms and queries
 - \circ $\,$ To run the search
 - To provide the search results in relevant format such as .txt and .doc files
- Expectations and responsibilities of the EAU GO
 - To oversee all logistics of the review process
 - To arrange phase 1 and phase 2 workshops
 - To assist the submission of the Systematic Review Report to peer reviewed journals
 - To assist with paper retrieval, when required

DEVELOPING RECOMMENDATIONS STATEMENTS FOR THE EAU GUIDELINES

1. Sourcing the Evidence

The evidence which will inform the recommendation statements is determined by the panels and will most often fall into these categories:

- A systematic review
- Studies identified through structured literature searches (scoping exercise)
- Studies discussed in the guideline text (identified previously or contemporaneously by panel expertise)

The sources of evidence will greatly influence the ability to rate the quality of that evidence, which is critical when developing the recommendation strength. Evidence that has been formally assessed with a systematic review will likely have an evidence quality rating already assigned. Evidence that has not undergone systematic review must by default be considered as lower in quality, because there has not been a formal risk of bias assessment performed on it. This is not a judgment on the true quality of such studies, but rather on the uncertainty.

1.1 Incorporating new information from an EAU GO systematic review

- The evidence for a particular recommendation or set of recommendations should ideally be obtained from a systematic review following the standard process outlined by the EAU Guidelines.
- Because this process starts with defining the question (using the "PICO" format"), there will already be familiarity with the background knowledge and deficits which informed the need for the review. These pieces of information ("why was the review undertaken") are ideally suited to supplement the text section of the guideline and should be summarized as appropriate.
- Following the text section is the "Summary of Evidence" table which takes the results from the systematic review and presents them in a succinct and accessible table. Additionally, the Summary of Evidence table for the guideline includes concerns about the evidence which are discovered through the systematic review, and which are brought forward by the panel's discussions. These concerns would include the overall quality of the evidence, the balance of benefit to harm and uncertainties about how patients might value the intervention despite the evidence. Details of these concerns or conflicts to the evidence can be highlighted in the text of the guideline and summarized in the table. It should be noted that for guideline purposes, the systematic review provides the synthesis of all the evidence and uncovers concerns about the evidence. Only these few components of the systematic review need go into the guideline text and summary table.

1.2 Incorporating prior information from an EAU Guideline text

- For recommendations which are not based on a systematic review, a narrative review of the important evidence which the recommendation will rely on should be present in the text section, and should be adapted for the Summary of Evidence table. Likewise, summary statements included in the Summary of Evidence table should be supported by prior comments within the text.
- For existing guidelines which do not undergo a new systematic review, this will be an iterative process of back and forth checks to assure appropriate components are in both the text and summary sections. Some text items may no longer be needed once this process is complete. Concerns and conflicts to the evidence can be included in the text and table in the same manner as when a systematic review is available.

2. Building the recommendation: EAU Adapted Evidence-to-Recommendation Framework

Certain elements combine to contribute to the overall recommendation statement and the strength it carries. These elements are:

- 1. The overall quality of the evidence which exists for the recommendation.
- 2. The magnitude of the effect (individual or combined effects).
- 3. The certainty of the results (having to do with precision, consistency, heterogeneity and other statistical or study related factors).
- 4. The balance between desirable and undesirable outcomes.
- 5. The impact of patient values and preferences on the intervention.
- 6. The certainty of those patient values and preferences.

Information on some or all of these elements may be available for each recommendation statement. The Strength Rating Form highlights these elements and informs how they are used to determine the recommendation strength, providing a workflow for the panels and transparency to the process.

Obtaining these elements should be as follows, and can be found in the Strength Rating Form:

1. Overall certainty of evidence: The confidence in effect estimates is obtained through the

analysis of several factors such as the study design, risk of bias (study quality), consistency of results across studies, precision of results or the applicability of results to the population of interest.

- 2. Balance of benefit and harm (desirable and undesirable effects): to be determined through discussion amongst the panel of experts and patient representatives (Appendix B).
- 3. Patient values and preferences: to be determined by the panel of experts and patient representatives

The Strength Rating Form provides a place for the final recommendation statement. The strength rating is assigned based on the balance of the above elements as determined by the panel. That decision making process can be explained as well on the form. There is also a space to include knowledge gaps and suggestions for future research.

3. Phrasing the Recommendation Statement

- Once the Summary of Evidence table has been constructed, the final recommendation should flow naturally from it, incorporating all the elements into a single statement. The summary and the recommendation are complementary. The summary provides a critical assessment of the evidence, the strength rating form adds the key elements needed to make a recommendation, and the recommendation finalizes the information into an action.
- Guideline recommendation statements are intended to provide guidance and should therefore be actionable. They should tell the reader what to do, to whom, under what specific circumstance, using unambiguous language, in a way that is implementable and ideally, measurable.
- With these goals in mind, and acknowledging that there is no perfect way to standardize phrasing of recommendations, statements should lead with a verb and avoid qualifiers (e.g. phrases such as "indicated", "gold standard", "select cases"). When a panel feels it is absolutely necessary to use a modifier to the action, they will be limited to choosing "must", "should" or "may". Modifiers are seldom necessary, and are replaced instead by the strength rating which follows the recommendation statement.

4. Assigning the Strength of Recommendations

- Strength rating should be either "Strong" or "Weak".
- Judgements about the strength of the recommendation will be made for each recommendation statement by the expert panel members, following the strength rating form template.
- Again, the elements found on the form, which determine the strength of the recommendation include: 1) overall certainty of the evidence, 2) the balance of benefits and harms, 3) differences in patient values and preferences, or uncertainty about them.
- Each element informs the strength rating judgement in this way:
 - Overall certainty of the evidence: higher quality and certainty evidence, and sometimes large effect size, leads to a strong rating. Low quality or absent evidence leads to a weak rating. The evidence should be weighted by at least 50%.
 - Balance of benefit to harm: a higher ratio of benefit to harm leads to a strong recommendation. A more equivalent ratio (i.e. greater harm) potentially leads to a weak rating.
 - Differences in patient values and preferences, or uncertainty of these: general acceptance of the treatments and harms within the patient population, and certainty of these values, leads

to a strong rating. Widely different values within the patient population regarding acceptance of a treatment or its associated harms, or uncertainty about patient values, leads to a weak rating.

• Costs and resource utilization: these considerations are important for certain guideline organizations. Within the EAU, cost is too broad a factor to include for consideration within the guidelines. However, if an intervention will have a significant impact on the European healthcare system, a panel may wish to include consideration of this in the rating.

Appendix Folder – Templates

- TEMPLATE 1 Effectiveness and Harms of Interventions: Literature Search/Systematic Review Requests by EAU Guideline Panels
- TEMPLATE 2 Diagnostic Test Accuracy Reviews: Literature Search/ Systematic Review Requests by EAU Guideline Panels
- TEMPLATE 3 Prognostic Factor Reviews: Literature Search/ Systematic Review Requests by EAU Guideline Panels
- TEMPLATE 4 Observational epidemiological review: Literature Search/ Systematic Review Requests by EAU Guideline Panels
- •
- •
- TEMPLATE 5 Protocol Template for a Systematic Review of Intervention Studies
- TEMPLATE 6 Protocol Template for a Diagnostic Test Accuracy Systematic Review
- TEMPLATE 7 Protocol Template for a Systematic Review of Prognostic factors
- TEMPLATE 8 Protocol Template for a Systematic Review of Prevalence and Incidence (Epidemiological Review)
- TEMPLATE 9 Protocol Template for a Systematic Review of IPD Prognostic Factor Study
- TEMPLATE 10 Full Report template for a Systematic Review of Intervention Studies
- TEMPLATE 11 Strength Rating form

All Templates can also be found on the Uroweb Dropbox (UROWEB DROPBOX \rightarrow 5. Documents for the associates \rightarrow 1. Templates)

REFERENCES

- Knoll T, Omar MI, Maclennan S, Hernandez V, Canfield S, Yuan Y, Bruins M, Marconi L, Van Poppel H, N'Dow J, Sylvester R. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the European Association of Urology. European Urology. 2018 Feb 1;73(2):290-300.
- 2. AMSTAR 2 Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.
- 3. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.
- 4. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011 Oct 18;155(8):529-36.
- 5. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of Internal Medicine. 2013 Feb 19;158(4):280-6.
- 6. Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, Staehler M, Powles T,

Ljungberg B, Bex A. Local treatments for metastases of renal cell carcinoma: a systematic review. The Lancet Oncology. 2014 Nov 1;15(12):e549-61.