KDIGO METHODS MANUAL FOR GUIDELINE DEVELOPMENT

VERSION 1
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Timeline

The timeline for a full *de novo* guideline is approximately two and a half years (from development of Scope of Work to publication of guideline) and includes two in-person Work Group (WG) meetings.

The KDIGO Executive Committee ranks guideline topics and agrees on the order in which they are developed or updated. Once a guideline has been selected, the KDIGO Co-Chairs outline the topic for guideline development and appoint the WG Co-Chairs. The WG Co-Chairs draft a preliminary Scope of Work and select WG members with domain expertise in multiple disciplines (e.g., nephrologists and non-nephrologists, nurses, social workers, dietitians, pharmacists, patients, etc.). After the WG is confirmed, KDIGO holds initial WG calls to fine-tune the Scope of Work for public review. The draft of the Scope of Work is then sent out for a public review comment period of one month. Based on feedback received from the public review, the WG finalizes the Scope of Work.

The Scope of Work is then used as the basis for a Request for Proposal (RfP), which is sent to known Evidence Review Teams (ERT). The teams have four to six weeks to submit their proposal. Each proposal is then reviewed by the KDIGO Co-Chairs, WG Co-Chairs, and KDIGO Guideline Development Director and Chief Scientific Officer for scientific merit and by the KDIGO Management team for the budget and other administrative details. The review, announcement of the selected ERT, and contracting take three to five weeks.

The chosen ERT develops the draft protocol with the initial set of key questions for the evidence review. The WG, led by the Co-Chairs, the ERT, and Method Committee representative, refine key questions, define Population, Intervention, Comparators, Outcomes, and Study Design (PICOS) criteria for those questions to be addressed in the evidence review, and tentatively assign certain topics for expert consensus, or summary of existing guidelines.

After the initial scoping review by the ERT, the KDIGO Co-Chairs, WG Co-Chairs, ERT, Methods Committee representative, and KDIGO team convene at Meeting Zero, which is the operational kickoff to the guideline development. The goal of this meeting is to finalize the protocol derived from the Scope of Work prior to the formal evidence review. The ERT provides instruction and leads discussion on the ERT process, the yield from scoping exercises and existing guidelines, the refinement of key questions, the matching of appropriate evidence types with questions of interest, the refinement of PICOS parameters, and the refinement of search criteria. During this meeting, the dates for the full WG meetings are decided and communicated to the WG members.

Between Meeting Zero and the first WG meeting, the ERT conducts the formal, systematic evidence review. The WG will be asked to review the evidence review deliverables, including screening results, data extraction forms, summary tables, and evidence profiles (EvP)/summary of findings (SoF) tables. All evidence review deliverables should be ready for the WG to review at least two weeks prior to the first WG meeting.

At this time, the KDIGO Methods Committee representative, the KDIGO team, and the ERT introduce the guideline format, including recommendation statements and practice points. For potentially suitable questions, the WG may begin the process of developing draft practice points and “straw dog” recommendation statements.

At the first WG meeting, the ERT leads a discussion of the evidence in summary tables and EvP/SoF tables. The WG members meet in small breakout groups based on guideline writing assignments to discuss the evidence, develop draft recommendations, review the initial practice points, and develop new statements as needed. Each small group then presents the statements and draft practice points for feedback from the full Work Group in attendance. A key goal at this stage is to ensure that the proposed practice points are appropriate and that the draft recommendation statements have a clear link to the evidence profiles.

Between the first WG and second WG meetings, the WG members write the supporting text (Key Information and Rationale) for each recommendation and refine practice points with supporting text or infographics, as appropriate. The WG Co-Chairs, Methods Committee representative, and KDIGO team review, edit, and comment on all draft sections, and the ERT finalizes evidence tables.

At the second WG meeting, the WG members again present the recommendations and practice points developed for their assigned topics to the WG group for discussion. Overall consensus is sought on the wording of guideline recommendations, grading of the strength of recommendations and certainty of evidence, practice points, and infographics. Voting is conducted as necessary and led by the WG Co-Chairs. Finally, everyone works to identify strategies for implementation: potential clinical performance measures, clinical tools for implementation, ancillary publications, etc.

After the second WG meeting, the WG members work to refine the recommendations, practice points, and supporting text. This guideline document undergoes several iterations between WG Co-Chairs, WG members, Methods Committee representative, and KDIGO team. Also, during this time, the ERT finalizes and submits the Methods Chapter and Data Supplement. The KDIGO team assembles the guideline draft and orchestrates organizational and public review. During the public review period, the ERT updates the literature search. Once all feedback from the public review has been collated and reviewed, the WG Co-Chairs, with the assistance of the WG Members, finalize any necessary revisions. The KDIGO team then prepares the guideline for publication in *Supplement to KI* and posting on the KDIGO website.

Critical path

The critical path collates the tasks, milestones, and timeline for guideline development. The critical path gives a roadmap to direct the WG through the process and helps to keep everyone on track. Progress is monitored by the KDIGO team and updated based on the completion of each task. Some tasks are done in parallel with other tasks.

The initial steps of the critical path are focused on administrative tasks such as the appointment of WG Co-Chairs and WG members, development and public review of the Scope of Work, and selection of the ERT, which take approximately five to seven months to complete (Table 1).

There are two different critical paths; one for *de novo* guidelines and one for an update to an existing guideline. Early in the guideline development process for an update, the KDIGO Co-Chairs and WG Co-Chairs review the previous guideline scope and decide if the update will be a partial update or a full rewrite. If a full rewrite is needed, then the *de novo* critical path is used. Since an update to an existing guideline usually has a circumscribed scope, face-to-face WG meetings may not be needed. Therefore, the update critical path can be adapted to remove one or both WG meetings, with the WG completing the work via teleconferences and email.

Table 1. Initial Steps of the KDIGO critical path

Initiation of the guideline development process
Appoint WG Chairs
Draft Scope of Work
Identify possible WG members and complete disclosure of interest/ confidentiality agreement
Chairs approve WG members based on the expertise needed (patients, related disciplines, Knowledge Translation Committee, etc.)
Invite WG members to join GL
Revise Scope of Work draft for Public Review with WG input/SONG
Public review of Scope of Work (targeted invitation to reviewers if needed)
WG and Chairs finalize the Scope of Work based on Public Review comments
Identification of ERT
Create RfP based on Scope of Work
Launch RfP
Review proposals and budget
ERT contract negotiation

ERT, Evidence Review Team; GL, guideline; WG, Work Group; RfP, Request for Proposals; SONG, Standardised Outcomes in Nephrology

Topic prioritization and selection

KDIGO frequently receives ideas and suggestions for guideline topics. They are analyzed by the KDIGO team and kept for further consideration. In most cases, that consideration happens at the second Executive Committee meeting of each year. At that meeting, potential topics are discussed and rated by the Executive Committee members. Executive Committee members may also suggest *de novo* guideline topics. Criteria for assessment include likely available evidence, disease burden, controversy or uncertainty, impact, stakeholder interest, and alignment or overlap with other KDIGO work. With the prioritized list, the KDIGO team explores possible timeframes for new topics after considering work that is planned or already underway. They make recommendations to the KDIGO Co-Chairs, who make the final decision to launch a guideline.

Role of Controversies Conferences

Guideline development may follow a KDIGO Controversies Conference on the same or a related topic. Conferences do not have as rigorous an approach to the evidence as a guideline. However, they often help in determining the scope of a guideline. They also can help establish the quantity of evidence published on the subject and identify ongoing trials that may provide additional evidence. Some attendees from a conference may serve on the subsequent guideline WG. A Controversies Conference can also help determine whether an update to a previous guideline is needed.

Stakeholder engagement

Introduction

According to Concannon et al., a stakeholder is “an individual or group who is responsible for or affected by health- and healthcare-related decisions that can be informed by research evidence.”[1]

In the guideline development context, engagement is defined as the “approach to gather input or contribution from stakeholders toward the development of a guideline, completion of any stages of a guideline, or dissemination, uptake or evaluation of a guideline and its recommendations.”[2]

Stakeholder engagement in guideline development enhances the relevance of the guidelines, creates a sense of ownership among stakeholders, and raises awareness about the project, ultimately facilitating acceptance, implementation, and adherence.[3, 4] It also contributes to the accountability and legitimacy of the guideline developers.[4] Stakeholder engagement requires careful planning in terms of whom to engage, at which steps of the guideline development process, at what level of engagement, and using which mode. The following sections address these four questions. In addition, practical guidance on facilitators for stakeholder engagement,

reporting on stakeholder engagement, and evaluation of stakeholder engagement are referenced.

Stakeholder types to engage

Concannon et al. have developed the 7Ps framework, which identified the following types of stakeholders: (1) patients and the public, (2) providers, (3) purchasers, (4) payers, (5) policy makers, (6) product makers, drug and device manufacturers, and (7) principal investigators.[1] Some types might be broadly defined. For example, the patients and the public type may include current and potential patients, their caregivers, families, and patient representatives (e.g., advocacy organizations).[1]

Table 2 below matches the above types of stakeholders to the types referred to in the KDIGO Methods Manual:

Table 2. Mapping of the 7Ps framework to the KDIGO process

Concannon typology	KDIGO typology
Patients and the public	Patients
Providers	Clinicians
Purchasers	
Payers	
Policy makers	Healthcare policy makers, public health organizations
Product makers, drug and device manufacturers	The industry
Principal investigators	Researchers

The type of stakeholders to represent will vary by the topic and the scope of the guideline effort. While it is typically important to engage patients and providers in clinically oriented guidelines, it is important to engage the public and policy makers in public health-oriented guidelines. Stakeholder “analysis” or “mapping” is one strategy to identify which stakeholder type to represent.[5, 6]

The selection of the types of stakeholders to engage should strike a balance between logistical capacity and the interests that need to be represented.

Identification of individual representatives

Identifying the individuals who will represent a specific stakeholder type requires time and effort. Guideline developers also need to establish ways to reach the different stakeholder groups of interest. Depending on the guideline topic and relevant stakeholder groups, some groups might be more difficult to reach than others. The GIN PUBLIC toolkit outlines some ways to reach patient and public groups. These include networks of patient advocacy groups and charities (e.g., Scottish Intercollegiate Guidelines Network's (SIGN) Patient and Public Involvement Network), health professionals and their organizations, the internet, and social media.[7]

There are seven highly desirable factors for health research teams to consider during the identification and invitation of individual representatives in a multi-stakeholder partnership, with the aim of forming equitable and informed teams: (1) expertise or experience, (2) ability and willingness to represent the stakeholder group, (3) inclusivity (equity, diversity, and intersectionality), (4) communication skills, (5) commitment and time capacity, (6) financial and non-financial relationships and activities, and disclosures of interest (DOI), (7) training support and funding needs. Additionally, three factors are desirable: influence, research-relevant values, and previous stakeholder engagement.[8]

With regard to "inclusivity", special consideration should be given to the engagement of under-represented groups.[2] The latter include those "who may experience health inequities for reasons such as a lack of inclusion in research, health policy, or guideline development; barriers to access of health services; or because of other socially stratifying factors." The latter have been described under the PROGRESS-Plus acronym.[2, 9, 10]

Steps in which to engage stakeholders

Stakeholders can be engaged at one or more steps of the guideline development process. Also, the steps at which engagement is desirable might vary by stakeholder group.

One could plan the engagement of the different stakeholders by deciding in which guideline groups to include them (e.g., WG including patients, ERT; Table 3). The specific tasks are then determined through the matrix showing each guideline group's different tasks in Table 4.

Table 3. Matrix of stakeholder types included in the different guideline groups

	Patients	Clinicians	Healthcare policy makers	Public health organizations	Industry	Researchers
Methods Committee						X
Work Group	X	X	X			
ERT	X	X	X			X
Peer reviewers	X	X	X	X		X
Knowledge Translation team	X	X		X		

ERT, Evidence Review Team

Table 4. Matrix of included parties in the various guideline steps (steps vs. groups)

Task	WG Co-Chairs	Work Group	Evidence Review Team	Methods Committee representative	Knowledge Translation Lead	KDIGO Staff
Prepare evidence review protocol and initiate scoping exercise						
Develop draft protocol(s)	x		x	x		x
Draft key questions	x		x	x		x
Call to discuss key questions and potential PICOS	x		x	x		x
Define PICOS	x		x	x		x
Draft analytical framework			x	x		
Assign section leads for specific topics/recommendations	x					
Formulate draft protocol(s) to include PICOS and proposed methodology			x			
Solicit WG feedback on and approval of draft protocol(s)	x		x			x
Discuss draft protocol(s) and rank outcomes	x	x	x	x		x
Revise protocol(s) based on WG feedback and final approval	x	x	x	x		x
Initiate scoping exercise	x		x	x		x
Conduct preliminary search			x			
Prepare review scoping exercise results and propose refinement	x		x	x		x
Disseminate protocol(s) based on the refinement	x	x	x	x		x
Refine protocol at Meeting 0	x		x	x		x
Review protocol(s) against AGREE II checklist				x		
Designate areas for potential Knowledge Translation tools	x		x	x		x
Send protocol(s) to WG for final review and comment			x			x
Clean and finalize protocol(s)	x	x	x			x
Register final protocol(s) on PROSPERO			x			
Send protocol(s) to KDIGO staff for posting on website			x			x
Conduct of evidence reviews						
Conduct systematic literature review			x			
Discuss statistical analysis plan	x	x	x	x		x
Evidence synthesis			x			
Preparation for drafting guidelines						
Review initial deliverables from systematic review	x		x	x		x
Systematic review deliverables reviewed by section lead	x	x				x
Section authors to review systematic review deliverables and specific questions related to the evidence base	x	x				x
Systematic review deliverables reviewed by additional non-section author	x	x				x
Revised review sent to section authors	x	x	x			x
Discuss and resolve any further questions on systematic review findings	x	x	x	x		x
Drafting the guideline						
Teleconference to introduce the format for writing guidelines	x	x	x	x	x	x
Write first draft of a single recommendation and chain of logic for approval by Co-Chairs, Methods representative, and KDIGO Staff	x	x	x	x		x
Provide feedback on format				x		x
Provide feedback on content	x					
Develop full set of draft ("strawdog") recommendations		x				
WG F2F Meeting One	x	x	x	x	x	x
Share agreed-upon recommendation statements from F2F Meeting						x
Develop the supporting text or draft graphics for each statement	x	x				x
Provide feedback on draft sections				x		x
Draft Quality of Evidence sections for all recommendation statements			x			
Reference supporting evidence profiles in all write-ups ensuring relevant profiles are called out in the text			x			

Task	WG Co-Chairs	Work Group	Evidence Review Team	Methods Committee representative	Knowledge Translation Lead	KDIGO Staff
Drafting the guideline (continued)						
Provide feedback on draft section	x					
Draft Methods Chapter for Guideline publication			x			
Collect information on outstanding issues, comments, and feedback for second F2F Meeting						x
Share all chapters with the WG for review prior to F2F Meeting						x
WG F2F Meeting Two	x	x	x	x	x	x
Come to consensus on guideline statements and supporting text	x	x	x	x		x
Call for voting on statements as necessary	x					
Develop Knowledge Translation tools for Guideline	x				x	x
After F2F, WG should finalize recommendations and write-ups	x	x	x	x		x
Review recommendation drafts for format and completeness				x		x
Final review from WG	x	x				
Complete reference management						x
Final signoff from WG Co-Chairs	x					
Prepare for Public Review						
Create Public Review forms						x
Post draft guideline and review forms for patients and health professionals						x
Send invite emails to external reviewers for the public review						x
Public Review						
Update evidence reviews			x			
Incorporate evidence from updated review into guideline	x	x	x			x
Feedback from Public Review						
Collate feedback from external reviewers						x
Identify top issues raised by external reviewers and propose solutions for each one	x		x	x		x
Send feedback to WG on the most difficult issues and proposed solutions						x
Summarize responses of top issues	x		x			x
Revise the guideline to address feedback from external reviewers	x	x	x	x		x
Distribute revised guideline to WG for review	x	x	x	x		x
Address the feedback provided by the WG	x		x	x		x
Merge and incorporate changes to prepare final guideline document						x
Final review of guideline against AGREE II checklist				x		
Final signoff from WG Co-Chairs	x					
Final evidence base lockdown (no additional publications may be added thereafter)			x			
Draft Executive Summary manuscript	x		x			x
Send Executive Summary to WG review and feedback		x				x
Revise Executive Summary based on WG feedback	x					x
Collect updated COI forms and bios						x
Obtain permission for tables and figures						x
Guideline submission to journal						
Submit guideline to the journal for approval						x
Respond to peer review and copyedited draft from journal	x		x			x
Review galley proofs	x	x	x			x
Implementation						
Development of implementation tools	x				x	x
Development of implementation research agenda	x				x	x
Development of visual algorithms for the guideline	x				x	x

AGREE, Appraisal of Guidelines for Research & Evaluation Instrument; F2F, face-to-face; KDIGO; Kidney Disease: Improving Global Outcomes; PICOS, Population, Intervention, Comparator, Outcomes, Study design; PROSPERO, International prospective register of systematic reviews; WG, Work Group

Level of engagement of stakeholders

Previous work has identified levels of stakeholder engagement,[11-14] which can be conceptualized as two levels: feedback and decision-making.

Mode of engagement of stakeholders

The mode of stakeholder engagement includes all routine communication channels as in-person meetings and virtual communication (telephone calls, emails, and web-enabled communications). They can also use group communications such as group discussions. Another mode of engagement is the passive mode, relevant to public comment (adapted from Concannon et al., 2018[11]).

Facilitators for stakeholder engagement

The following factors facilitate stakeholder engagement and contribute to achieving "meaningful" engagement (adapted from Armstrong et al., 2017,[15] and Magwood et al., unpublished):

- Pre-meeting readings and training
- Use of understandable speech and language
- Using smaller groups
- Lack of prior relationships between members of the group (e.g., patient and their doctor)
- Facilitators being skilled and experienced (e.g., to manage power dynamics within the group)
- Early involvement that is maintained throughout the process
- Early and clear specification of roles and expectations
- Adequate compensation (e.g., for time, travel, accommodation)

Reporting on stakeholder engagement

There is no available tool for reporting on stakeholder engagement. Developers can build on the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) reporting checklists (long-form and short-form versions), initially developed to report on the reporting of patient and public involvement in research.[16]

Evaluation of stakeholder engagement

There is no available evaluation tool for multi-stakeholder engagement. Developers can build on the Patient Engagement Evaluation Tool (PEET), which was initially developed and shown to be valid for clinical practice guideline development.[17]

Resources/checklists

- https://g-i-n.net/toolkit/
- MUSE project (in progress)[2]

Roles and responsibilities

Appointment of Guideline Co-Chairs and Work Group members

KDIGO Guideline WG Co-Chairs are selected and appointed by the KDIGO Co-Chairs. WG Co-Chairs must be able to work together, make decisions, run efficient meetings, handle disagreements, and commit to spending time writing and editing the guideline document. They must know that the guideline development process involves two and a half to three years of work, with the potential for continued work related to guideline updates when needed.

The WG Co-Chairs review the work involved, expertise needed, and time frame for the project as a guide for WG member selection. Potential candidates should be willing and able to do the work, have expertise in the topic area, and be available and able to devote the time. WG member selection should strive for a balance in geography, gender, age, and expertise/experience. Patient voice is also highly important for the guideline development process, particularly when discussing *Values and preferences*; therefore, all WGs must include at least two patient representatives. It is crucial to analyze the potential for perceived competing interests (financial and non-financial) and require full disclosures of any competing interests.

The determination as to whether a disclosed interest is a competing interest for guideline WG participants will involve application of this policy and careful judgment. Factors that may influence the judgment include the relevance of the interest to the guideline, as well as the nature, magnitude, and recency of the interest. Where interests do not fall discretely within the DOI management framework, decision-makers will also consider as an underlying principle how a particular interest might be reasonably viewed by a lay member of the public. An individual with a disease or condition (or who has a family member with that condition) is not regarded as having a competing interest solely because they have the condition.

DOI Review and Management

For KDIGO Co-Chairs, decisions and approval will be made by the Executive Committee.

For WG Co-Chairs, decisions on appropriate management will be made by the KDIGO Co-Chairs with advice from the Methods Committee, if necessary. The Co-Chairs will present their decisions for final approval to the Executive Committee.

For WG members, ERT personnel, and members of the Methods Committee or KT team, decisions on appropriate management will be made by the KDIGO team with advice from the Methods Committee, if necessary. The KDIGO team will present their decisions for final approval by the KDIGO Co-Chairs and will inform the WG Co-Chairs of their assessment.

To maximize objectivity and transparency of the adjudication process and management steps, the following decision matrix is used to classify interests as high-, moderate-, or low-risk (Table 5).

*Table 5. Decision matrix for the adjudication and management of competing interests**

Attributes	Examples	Management
High-risk		
Co-Chairs		
Active relationship with a high-risk entity (personal, specific, financial)	Ongoing role as a paid consultant for a pharmaceutical company which produces products that are relevant to the guideline topic	Divestiture of the interest or recusal from Co-Chair role.
Active relationship with a high-risk entity (non-personal, specific, financial)	Ongoing role as a paid consultant for a pharmaceutical company which produces products that are relevant to the guideline topic. Monies are paid to the Co-Chair's institution	If monies were paid to the institution rather than to the individual, management is at the discretion of the KDIGO team and may not require divestiture or recusal.
WG Members		
Active relationship with a high-risk entity (personal, specific, financial)	Potential WG member with an ongoing role as a scientific advisor for a pharmaceutical company which produces products that are relevant to the guideline topic	At the discretion of the KDIGO Team: (1) Divestiture of the interest or recusal from Work Group, or (2) Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Active relationship with a high-risk entity (non-personal, specific, financial)	Potential WG member has participated as a member of the Steering Committee for a relevant randomized trial, but all monies were paid to their institution	If monies were paid to the institution rather than to the individual, management is at the discretion of the KDIGO team and may not require divestiture or recusal
	The spouse of a potential WG member has an ongoing paid role as a scientific advisor for a pharmaceutical company which produces products that are relevant to the guideline topic	Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Moderate-risk		
Active relationship with a high-risk entity (personal, non-specific, financial)	Potential Co-Chair or WG member with an ongoing role as a paid consultant for a pharmaceutical company that produces products which are not relevant to the guideline topic	At the discretion of the KDIGO team, management may not be required
Active non-financial interest specific to a guideline topic or individual guideline statement	Co-Chair or WG member authored a clinical trial that is included in the evidence summaries for the guideline, or is currently participating as a member of the Steering Committee for a relevant randomized trial	Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Low-risk		
Active non-financial interest only partially specific to the guideline	For a guideline on pharmacological management of hypertension in CKD management, Co-Chair or WG member conducted survey research of the association between diet and blood pressure control. The research is not included or not likely to be included in the evidence summaries prepared by the ERT to support the guideline	Participates in all aspects of guideline development including discussions, voting, drafting statements, and authorship
Inactive financial interest specific to the guideline	Co-Chair or WG member held stock in a pharmaceutical company with products specific to the guideline topic but sold all shares a year ago	
Inactive, non-personal, financial interest specific to the guideline	Grant income received by the Co-Chair's or WG member's employer from the company that manufactures the product	

*For additional details, please see the section on Types of interest**.** and **Appendix A.**

Examples of competing interests and management CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; WG, Work Group

Management of competing interests is more stringent for WG Co-Chairs than for WG members. For example, both WG Co-Chairs are required to be free of high-risk, personal, and financial competing interests at the time they join the WG (Table 5). However, both WG Co-Chairs and WG members are required to refrain from initiating new high- or moderate-risk financial interests during the period of guideline development.
of any competing interests.

The KDIGO team is tasked with the overall project management of the guideline development and assists WG Co-Chairs and WG members throughout the process. They organize the meetings and calls and liaise with KDIGO Leadership and the ERT. They advise the volunteers on the process and timeline for the guideline development. They create the critical path, track the guideline development progress, and monitor deliverables to ensure the project stays on target. They also review guideline drafts, collate, and organize input from the two public comment periods, and prepare the guideline manuscript for submission to the journal.

Role of Methods Committee representative

A guideline WG includes a member of the KDIGO Methods Committee to advise on KDIGO methods as presented in the Methods Manual. The Methods representative serves as a methodologic advisor to the WG members to answer any questions about methods, such as those related to the evidence reviews, the GRADE system for grading the certainty of evidence and strength of recommendations, and the appropriate use of practice points. The Methods representative also reviews guideline drafts for format and clarity.

Role of Knowledge Translation lead

A Knowledge Translation (KT) lead will be appointed to each guideline. The primary role of this person is to develop the most useful tools for dissemination and implementation of the guideline while it is being developed. The KT Lead may be a member of each WG or an external volunteer appointed by KDIGO.

Possibilities for the KT team to consider include: How does clinical practice vary among and between regions? How might these differences affect the potential usability and uptake of the guidance? What Knowledge Translation tools may be needed to support the guideline? Apart from the need for translation into different languages, how might these tools vary among and between regions? Are there effective tools that other developers have used to facilitate implementation of similar guidance?

Approval processes

The KDIGO Executive Committee annually reviews and discusses potential new guideline topics and previous KDIGO guidelines where new evidence has signified that an update is needed. The KDIGO Executive Committee (led by the KDIGO Co-Chairs) selects and approves

the guideline lineup. Once the lineup is confirmed, the Executive Committee is not sought for further approval regarding guideline content. The KDIGO Co-Chairs ultimately make the final decision to launch a guideline.

After the KDIGO Executive Committee has approved a guideline topic, the KDIGO Co-Chairs will approve and appoint the WG Co-Chairs. The WG Co-Chairs then present a list of potential WG Members to the KDIGO Co-Chairs for their review. Formally the KDIGO Co-Chairs approve and appoint the WG Members as well.

Once appointed, the WG, led by the WG Co-Chairs, has full control of and assumes full responsibility for the guideline content and has the final say on decisions pertaining to guideline development. At different points in the process, the WG members approve the content at face-to-face WG meetings and via email. Once the guideline is finished and ready for publication, the WG Members sign an *Assignment of Rights* form stating that KDIGO will be the sole and exclusive owner of all rights in the guideline. KDIGO accepts these signed forms as the approval that the WG has finalized the content and it is ready for publication. All KDIGO WGs have responsibility for the final content in the guideline, ancillary publications, and implementation/knowledge translation tools derived thereof.

Disclosures of interest

Ensuring the trustworthiness of clinical guidelines is central to the KDIGO mission of improving care and outcomes of patients with kidney disease. In line with other international organizations, KDIGO follows defined processes for DOI and management of competing interests.

Underlying principles and key definitions

Types of interest

Interests can be **specific** or **non-specific** and **financial** or **non-financial**. An interest is “specific” if it refers directly to the matter under discussion. An interest is “non-specific” if it does not refer directly to the matter under discussion.

Financial interests refer to anything of significant monetary value and can be personal or non-personal. A non-exhaustive list of financial interests includes:

- Research grants
- Stock or equity interest
- Employment
- Consultancy
- Membership on Advisory Boards or Steering Committees
- Speaking fees
- Funding for travel
- Payment for manuscript preparation
- Expert testimony

- Patents/royalties
- Receipt of gifts, favors, or hospitality

A **personal** financial interest is one where there is or appears to be opportunity for personal financial gain or financial gain to a family member. For the purposes of this policy, a family member is defined as a partner, spouse, dependent, or other relative living within the same household as the participant for a year or longer.

A **non-personal** financial interest is one where there is or appears to be opportunity for financial gain or other benefit to a department or organization in which the individual is employed but which is not received personally.

A **non-financial interest** refers to "any non-financial professional or personal benefit, or non-financial issue that could affect one's perceived objectivity." Such interests could include the desire for prestige, power, or faculty advancement; interest in obtaining positive results; or relate to personal, political, academic, ideological, and/or religious views.

Although financial and non-financial interests of professional colleagues, friends, and family members outside of the household can theoretically bias a guideline participant, attempting to adjudicate these interests would be unreasonably cumbersome and intrusive; hence, the DOI process does not solicit such information from people outside the participant's household. Similarly, KDIGO does not ask participants to disclose political, religious, or personal beliefs, nor consider these relevant to the DOI process.

Factors considered in adjudicating seriousness of DOI[1]

The threat to guideline integrity posed by any given interest is highest if it is **active** at the time of guideline development (e.g., holding stock in a pharmaceutical company that might stand to benefit from the guideline) and would be expected to decrease over time after that interest has been divested. An active, personal, financial interest specific to the guideline topic would be considered high-risk, while an active non-financial or non-specific financial interest might be deemed moderate risk. Any interests that have been **inactive** for >24 months from guideline initiation are considered low risk.

As recently proposed by the American College of Physicians Clinical Guidelines Committee, KDIGO also recognizes the significance of the type of entity with whom a participant might have a relationship. **High-risk entities** are those with a direct financial stake in the guideline topic or statements, and include pharmaceutical and biomedical device companies, public payors, insurers, and patient advocacy groups. Since most of these types of organizations engage in broadly ranging products, services, and disease areas, it can be difficult to adjudicate their clinical relevance (specificity) to a given guideline topic. As such, a participant's active

[1]Adapted from the ACP guideline for DOI-COI management18. Qaseem A, Wilt TJ, Clinical Guidelines Committee of the American College of P, *et al.* Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med* 2019; **171:** 354-361.

relationship with a high-risk entity is considered a potentially serious threat to guideline integrity and is classified as high-risk. However, there are scenarios that warrant special consideration on a case-by-case basis. Since patient advocacy groups focus on specific clinical disorders, ascertaining their relevance to a guideline topic is straightforward, and relationships with such entities unrelated to a guideline topic are not considered a significant risk. Similarly, when participants have relationships with early-stage pharmaceutical or medical device companies with a clearly defined narrow product pipeline or focus, it may be reasonable to adjudicate these interests as low-risk if they are clearly unrelated to a guideline topic.

If, in specific circumstances, adherence to the policy outlined in this manual is not possible, appropriate measures will be taken to minimize the risk of the conflict in question. KDIGO will always strive to be as pragmatic and transparent as possible.

Participants in the DOI process

KDIGO requires disclosure and transparency regarding competing interests of all people working on KDIGO products, including:

Guideline production team

- All WG members
- Clinical/methodologists and/or information scientists/librarians contributing to analysis of literature, including ERT members, members of the Methods Committee, and members of the KT team for each guideline.
- KDIGO team involved with the guideline under development

Guideline leadership

- Guideline WG Co-Chairs

KDIGO leadership

- Members of the KDIGO Executive Committee
- KDIGO Co-Chairs

Types of interest subject to the DOI process

Financial interests

The purpose of these disclosures is to collect information on financial benefits (personal or non-personal, see Appendix A. Examples of competing interests and management). Any financial interest representing >€500 per entity per year must be disclosed annually for all parties involved in guideline development and dissemination (including WG Chairs, WG members, ERT members, members of the Methods Committee, and members of the KT team) as well as members of the Executive Committee.

The window for disclosures begins 24 months before Meeting Zero. For example, for a WG that held Meeting Zero on January 1 and finished its work on December 1, the 24-month window for disclosure would apply to relationships accrued during the period beginning 24 months before January 1 and end on December 1.

KDIGO asks that all those involved in guideline production will avoid new interests while the guidelines are being developed. If new interests develop, they should be disclosed immediately.

Non-financial interests

WG members are selected for their expertise, and therefore it is expected that many members will have previous activities that are conceptually linked to their work on the guideline. The intent is not to disqualify all members with any related experience, but to ensure that WG members have (and are perceived to have) the necessary objectivity to produce balanced, rigorous guidance.

Examples of relevant non-financial interests include:

- Involvement in an ongoing or scheduled trial or research project aimed at determining the effectiveness of a matter under review
- Having authored or co-authored a document that has been included in ERT evidence summaries and so will be considered in drafting the guideline

Evaluation of non-financial interests will require careful judgment as to whether they might be prejudicial to an objective interpretation of the evidence. The fundamental questions to be asked when assessing these interests are (1) whether they lead to “a non-financial professional or personal benefit, such as increasing or maintaining their professional reputation” for the WG member, and (2) whether they may impact an individual’s ability to approach a scientific question with an open mind.

For example, a WG member who led a clinical trial showing that drug A is beneficial might derive considerable professional benefit if drug A were then recommended as the first-choice treatment in KDIGO guidance on condition X. In contrast, a WG member who wrote a review article on condition X might not necessarily have a relevant non-financial interest, unless the article took an unusually strong position on drug A or an alternative. Appendix A. Examples of competing interests and managementprovides additional detail.

DOI process

The KDIGO Disclosure of Interest form is presented in Appendix B. Disclosures of interest form Initial disclosures will be collected at the time of:

- Appointment of members of the guideline production team
    - KDIGO Co-Chairs
    - WG Co-Chairs
    - WG members
    - ERT

    - Members of the Methods Committee and KT team
- Appointment of members of the Executive Committee and Methods Committee
- Appointment of KDIGO Co-Chairs

The process will be mentioned in all KDIGO appointment letters (e.g., WG, Executive Committee, Methods Committee), and disclosures will be collected at that time. Policies for collecting initial disclosures will be managed by the KDIGO team. Disclosures will be updated annually for all those involved in KDIGO activities.

Disclosures should be updated before each WG meeting or annually for entities not connected to a particular guideline (e.g., Executive Committee, KDIGO Co-Chairs).

- Disclosure and discussion of competing interests at the start of each WG meeting
- Inclusion of the most recent version of the disclosure statements in:
    - The public review of the document,
    - The published guideline or update; and
    - Any presentations given by WG members, or by others involved in the production or dissemination of guidelines (e.g., ERT members, members of the Methods Committee, and members of the KT team)

The agenda for every WG meeting includes an update of WG disclosures prior to the start of every meeting. Prior to each meeting, the WG Co-Chairs will review the disclosures and determine which course of action is required for any specific WG member (Table 4). A list of all disclosures will be circulated to all WG members along with the agenda, and each member will speak to her/his disclosures at the start of each WG meeting.

WG members should not publicize their appointment to the guideline Work Group, although they may discuss it with individuals at their institution, such as department head or division chief. Should new interests arise during guideline development, they should be disclosed to KDIGO staff and the WG Co-Chairs immediately.

Management of competing interests

Managing organizational competing interests

To minimize the risk of organizational competing interests, KDIGO does not solicit or accept funding from for-profit entities for guidelines, and KDIGO staff who raise funds from industry do not attend WG meetings or interact with WG members. All industry funders of any aspect of KDIGO work (past and present) are listed on the KDIGO website.

Managing competing interests among guideline participants

The determination as to whether a disclosed interest is a competing interest for guideline WG participants will involve application of this policy and careful judgment. Factors that may influence the judgment include the relevance of the interest to the guideline, as well as the

nature, magnitude, and recency of the interest. Where interests do not fall discretely within the DOI management framework, decision-makers will also consider as an underlying principle how a particular interest might be reasonably viewed by a lay member of the public. An individual with a disease or condition (or who has a family member with that condition) is not regarded as having a competing interest solely because they have the condition.

DOI Review and Management

For KDIGO Co-Chairs, decisions and approval will be made by the Executive Committee.

For WG Co-Chairs, decisions on appropriate management will be made by the KDIGO Co-Chairs with advice from the Methods Committee, if necessary. The Co-Chairs will present their decisions for final approval to the Executive Committee.

For WG members, ERT personnel, and members of the Methods Committee or KT team, decisions on appropriate management will be made by the KDIGO team with advice from the Methods Committee, if necessary. The KDIGO team will present their decisions for final approval by the KDIGO Co-Chairs and will inform the WG Co-Chairs of their assessment.

To maximize objectivity and transparency of the adjudication process and management steps, the following decision matrix is used to classify interests as high-, moderate-, or low-risk (Table 5).

*Table 5. Decision matrix for the adjudication and management of competing interests**

Attributes	Examples	Management
High-risk		
Co-Chairs		
Active relationship with a high-risk entity (personal, specific, financial)	Ongoing role as a paid consultant for a pharmaceutical company which produces products that are relevant to the guideline topic	Divestiture of the interest or recusal from Co-Chair role.
Active relationship with a high-risk entity (non-personal, specific, financial)	Ongoing role as a paid consultant for a pharmaceutical company which produces products that are relevant to the guideline topic. Monies are paid to the Co-Chair's institution	If monies were paid to the institution rather than to the individual, management is at the discretion of the KDIGO team and may not require divestiture or recusal.
WG Members		
Active relationship with a high-risk entity (personal, specific, financial)	Potential WG member with an ongoing role as a scientific advisor for a pharmaceutical company which produces products that are relevant to the guideline topic	At the discretion of the KDIGO Team: (1) Divestiture of the interest or recusal from Work Group, or (2) Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Active relationship with a high-risk entity (non-personal, specific, financial)	Potential WG member has participated as a member of the Steering Committee for a relevant randomized trial, but all monies were paid to their institution	If monies were paid to the institution rather than to the individual, management is at the discretion of the KDIGO team and may not require divestiture or recusal
	The spouse of a potential WG member has an ongoing paid role as a scientific advisor for a pharmaceutical company which produces products that are relevant to the guideline topic	Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Moderate-risk		
Active relationship with a high-risk entity (personal, non-specific, financial)	Potential Co-Chair or WG member with an ongoing role as a paid consultant for a pharmaceutical company that produces products which are not relevant to the guideline topic	At the discretion of the KDIGO team, management may not be required
Active non-financial interest specific to a guideline topic or individual guideline statement	Co-Chair or WG member authored a clinical trial that is included in the evidence summaries for the guideline, or is currently participating as a member of the Steering Committee for a relevant randomized trial	Participates in all discussion but is recused from decision-making and drafting of related guideline statement(s); can participate fully in all other guideline statements that are not specific to their interest
Low-risk		
Active non-financial interest only partially specific to the guideline	For a guideline on pharmacological management of hypertension in CKD management, Co-Chair or WG member conducted survey research of the association between diet and blood pressure control. The research is not included or not likely to be included in the evidence summaries prepared by the ERT to support the guideline	Participates in all aspects of guideline development including discussions, voting, drafting statements, and authorship
Inactive financial interest specific to the guideline	Co-Chair or WG member held stock in a pharmaceutical company with products specific to the guideline topic but sold all shares a year ago	
Inactive, non-personal, financial interest specific to the guideline	Grant income received by the Co-Chair's or WG member's employer from the company that manufactures the product	

*For additional details, please see Appendix A. Examples of competing interests and management.
CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; WG, Work Group

Management of competing interests is more stringent for WG Co-Chairs than for WG members. For example, both WG Co-Chairs are required to be free of high-risk, personal, and financial competing interests at the time they join the WG (Table 5). However, both WG Co-Chairs and WG members are required to refrain from initiating new high- or moderate-risk financial interests during the period of guideline development.

Development of Scope of Work

Co-Chairs and Work Group involvement

The process begins with a conference call, which includes the KDIGO Co-Chairs, the KDIGO team, and the newly appointed WG Co-Chairs. During this call, the process of guideline development used by KDIGO is discussed. The first tasks are described. The WG Co-Chairs then discuss and arrive at a list of potential volunteer WG members, again looking for balance, a commitment to writing, and the ability to devote the time required. The WG members are chosen by the WG Co-Chairs with input from KDIGO Leadership. Together, the WG Co-Chairs and the WG members write the first description of the project, including preliminary versions of all relevant key questions, called the Scope of Work.

Public Review

One of the singular features of the KDIGO guideline development process is the open public review phase. When the Scope of Work is in near final form, all stakeholders have an opportunity to make comments and suggestions. This is one of two opportunities for any stakeholder to inform the development of KDIGO guidelines. Comments are sought from researchers and clinicians, industry, patients, other public health organizations, and healthcare policy makers. A full month is usually allowed for this comment period but may be shortened or extended if deemed necessary by KDIGO.

The process involves sending a link to interested persons identified by KDIGO and public posting of the link to the KDIGO website. That link has a form for review, and all the comments are processed by the KDIGO team and sent to the WG Co-Chairs. Every comment is given consideration by the WG Co-Chairs to determine if changes to the document are necessary, but a point-by-point response document is not required. The approach to this latter point is determined by the WG Co-Chairs.

Stakeholder engagement could be enhanced through additional methods:[19]

- Assembling a panel of stakeholders (e.g., public panel)
- Consultation with stakeholder group(s)
- Using a quantitative or qualitative approach to explore stakeholder views
- Public comment

Different approaches have been shown to be complementary,[20] hence, a combination of these approaches is desirable when feasible.

Evidence Review Team selection process

The KDIGO guideline development process calls for an outside, independent ERT. This group is vitally important and carefully selected.

Request for proposals

Using the first draft of the guideline Scope of Work, the KDIGO team prepares a Request for Proposals (RfP). The RfP is then sent to all the relevant institutions with known expert evidence review and synthesis.

Proposal section requirements

Four to six weeks are allowed for the institution to submit a proposal which must contain the following components:

- Staff to be assigned to the guideline project and identification of the project lead
- Relevant experience, particularly in nephrology, and curriculum vitae (CVs) for the proposed team
- Proposed methods for evidence review, critical appraisal, and evidence synthesis to complement the guideline development on a specific topic
- Administrative details from each institution
- Budget and estimated timeline

Proposal review process

The KDIGO team first reviews the proposals and makes a preliminary determination of viable candidates. The proposals are then sent to the KDIGO Co-Chairs, WG Co-Chairs, and KDIGO Guideline Development Director and Chief Scientific Officer for review of their scientific merit. The budget and administrative details are reviewed by the KDIGO Chief Executive Officer and Chief Operating Officer. Conference calls may be arranged with everyone involved to discuss the merits of the ERTs under consideration. The decision will be made through votes from the KDIGO Co-Chairs, WG Co-Chairs, and KDIGO Chief Executive Officer.

ERT selection and contract negotiations

Once a preliminary decision is made, a draft contract is written, and an on-site visit by the KDIGO team may be arranged. Agreement is reached on the contract details, including deliverables, timeline, and payment schedule. Upon agreement, the contract is signed by the KDIGO Chief Executive Officer.

A major factor in the relationship with an ERT is mutual understanding of the Scope of Work and milestones by which progress can be assessed. Although independent, the ERT is accountable to the WG Co-Chairs for scientific issues and the KDIGO team for administrative issues.

Evidence review process

The systematic evidence review and guideline development process consist of multiple steps. These steps are not always sequential, some can happen in parallel, and some may require an iterative process before making final decisions. The WG is an independent group of experts responsible for developing the guideline after carefully reviewing the evidence provided by the ERT and by following the KDIGO guideline development process. This process includes the following steps.

Draft the evidence review protocol(s)

The evidence review protocol is developed by the ERT based on the final Scope of Work. The WG Co-Chairs and WG members will review and provide feedback to ensure the evidence review will address all topics required for the guideline development. The protocol includes the key questions, associated analytic framework, PICOS criteria (the inclusion and exclusion criteria used to identify studies), methodology for screening and data extraction, the proposed plan for evidence synthesis, and describes the deliverables for the presentation of the data.

Identify key questions

Questions of interest are directly linked to the analytic framework, guide the evidence review, and are formulated according to the PICOS criteria. PICOS refers to **P**opulation, **I**ntervention, **C**omparator, **O**utcomes, **S**tudy design. Other criteria may also be added, such as setting or timing (of intervention and/or of outcome measurement). For guideline updates, new key questions may be required, depending on gaps in the evidence identified in the previous review or new evidence published in the interim.

Well-defined key questions will include most elements of the PICOS criteria. For example:

- In patients with X, what are the long-term effects of treatment Y compared with treatment Z on outcomes A, B, and C?
- What are the short-term harms of treatment Y compared to treatment Z in patients with X?

Three types of PICOS criteria may be helpful in understanding decisions that need to be made at different stages in the review:

- The **review PICOS** (planned at the protocol stage) is the PICOS on which the eligibility of studies is based (what will be included and excluded from the review).
- The **PICOS for each synthesis** (also planned at the protocol stage) defines the question that the specific synthesis aims to answer, determining how the synthesis will

be structured, specifying planned comparisons (including intervention and comparator groups, any grouping of outcome, and population subgroups).
- The **PICOS of the included studies** (determined at the review stage) is what was actually investigated in the included studies.

Key question prioritization

The WG should prioritize PICOS questions using the following steps

- Brainstorming PICOS questions: In this step, the WG is encouraged to document all potential questions that may be of interest to different end users of the guidelines.
- Prioritizing PICOS questions: If the scope of the guideline proposed is very broad, the WG may go through a formal process of prioritization of the suggested questions. This step will require consultation with the WG Co-Chairs and surveying the WG itself. It is important to have a discussion around the criteria that will determine priorities (e.g., PICOS questions with new, practice-changing evidence or those with considerable variability in practice).
- Finalizing PICOS questions: After the prioritization exercise, the WG should make decisions about which PICOS questions are:
    - likely to lead to formal recommendations
    - important for implementation considerations
    - considered good practice in which the alternative would be ridiculous or unacceptable

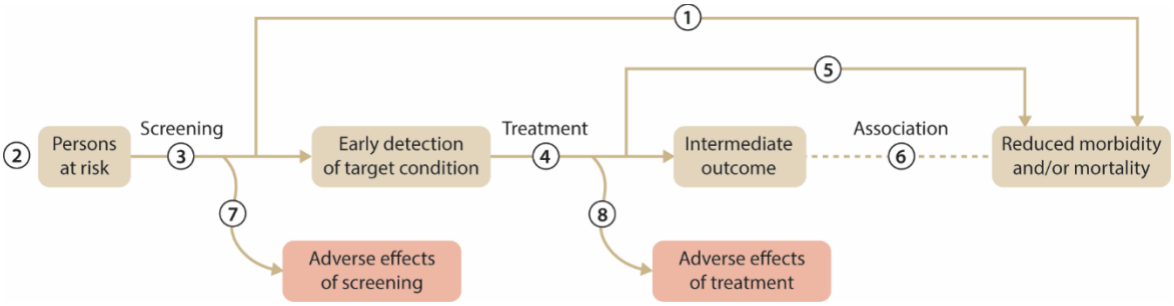
Design analytic framework

The analytic framework links populations, interventions, and outcomes to help structure the evidence review. All key questions for the evidence review(s) should be listed in an analytical framework.

- The population consists of patients for whom the proposed action is intended (i.e., persons at risk).
- Actions (e.g., screening, treatment) are depicted by arrows and link the population to the outcomes or link outcomes directly. The name of each action appears in a label above its respective arrow.
    - Each arrow is associated with a key question that must be addressed by the evidence review.
- Outcomes are depicted by rectangles. An analytic framework distinguishes between critical and important outcomes. All critical and important clinically relevant outcomes must be specified. If important outcomes are included in the evidence review, their relationship to the clinically relevant outcome is depicted with a dashed arrow.
    - Adverse events are denoted by curved arrows and can also appear in the framework.

Figure 1 shows the template for the analytic frameworks used in the development of KDIGO guidelines. The framework shows (from left to right) the population (i.e., persons at risk), actions (i.e., treatment), the critically important and important outcomes, and the desired associations between key questions. Each element in the flowchart is related to one or more key questions (depicted as numbered ovals).

Figure 1. Template for analytic framework



Initiate scoping exercise

Output from the scoping exercise provides an overview of the evidence (including areas where evidence is lacking) and helps to establish what the guideline will include and what will not be covered by the evidence review. The primary goal is to identify key literature that the WG Co-Chairs and members can use to inform to answer relevant PICOS questions and help to prioritize and select the deliverables for the ERT. The output from the exercise is a summary of the evidence, a list of key studies, guidance that the WG is expected to read and understand, and a comparative analysis of relevant guidance from other organizations, as well as prior guidance from KDIGO, if relevant. The findings from this exercise will inform Meeting Zero discussions regarding the refinement of PICOS criteria as described in the final protocol.

Identify eligible study designs

The appropriate study design will vary according to the review question and should be considered and stated when writing the evidence review protocol(s), as well as the approach to decisions on the hierarchy of study designs (Table 6; as decided at Meeting Zero). The WG should consider what question they want to answer, what study design is most appropriate to answer that question, and what the likely availability of evidence is. Table 6 provides a general guide for the most appropriate study design for a range of types of review and the usual hierarchy in the level of published evidence applied.

Table 6. Study designs by type of review

Review type	Intervention review	Diagnostic accuracy review	Risk prediction tool review	Prognostic risk factor review	Qualitative evidence synthesis
Hierarchy ↓	RCTs*	Prospective or retrospective cohort studies (cross-sectional design)	Cohort studies (including those with external validation)	Prospective cohort studies [RCTs may also be appropriate]	Qualitative studies with or without thematic analysis
	Comparative cohort studies	Case-control studies*†		Retrospective cohort studies	Consider including surveys with open-ended questions
	Case-control studies			Case-control studies	
	Cross-sectional studies				
	Case series, case reports				

RCT, randomized controlled trial

*If the intervention review focuses on harms, cohort studies are likely to be more appropriate, and non-comparative cohort studies may also be considered.

†Studies that compare the results of the index test in patients with an established diagnosis with its results in healthy controls. Only considered appropriate in rare cases.

The choice of the most appropriate type of evidence can also be thought of by considering what the question is aiming to inform. Table 7 presents the suggested review approach for some common question types.

Table 7. Suggested review approach for common question types

Aim of question	Suggested review approach
Effectiveness of an intervention	Intervention review – as per Table 6.
Harms from an intervention/risk of harm	Non-randomized studies are likely to be the most informative type of data with long term follow-up. This may also include non-comparative studies.
Accuracy of a diagnostic test	Diagnostic accuracy review – as per Table 6.
Accuracy tool to predict disease progression	Risk prediction tool review – as per Table 6.
Identifying factors that may be associated with progression or a disease	Prognostic risk factor review – as per Table 6.
Cost-effectiveness	Cost-effectiveness analyses based on RCTs may be identified. If not, surveys on costs or data from registries may be used.
Baseline risk	Natural history studies and epidemiological studies.
Patient opinion or barriers and facilitators	Usually, this is best informed by a qualitative review or mixed-methods approach.

RCT, randomized controlled trial

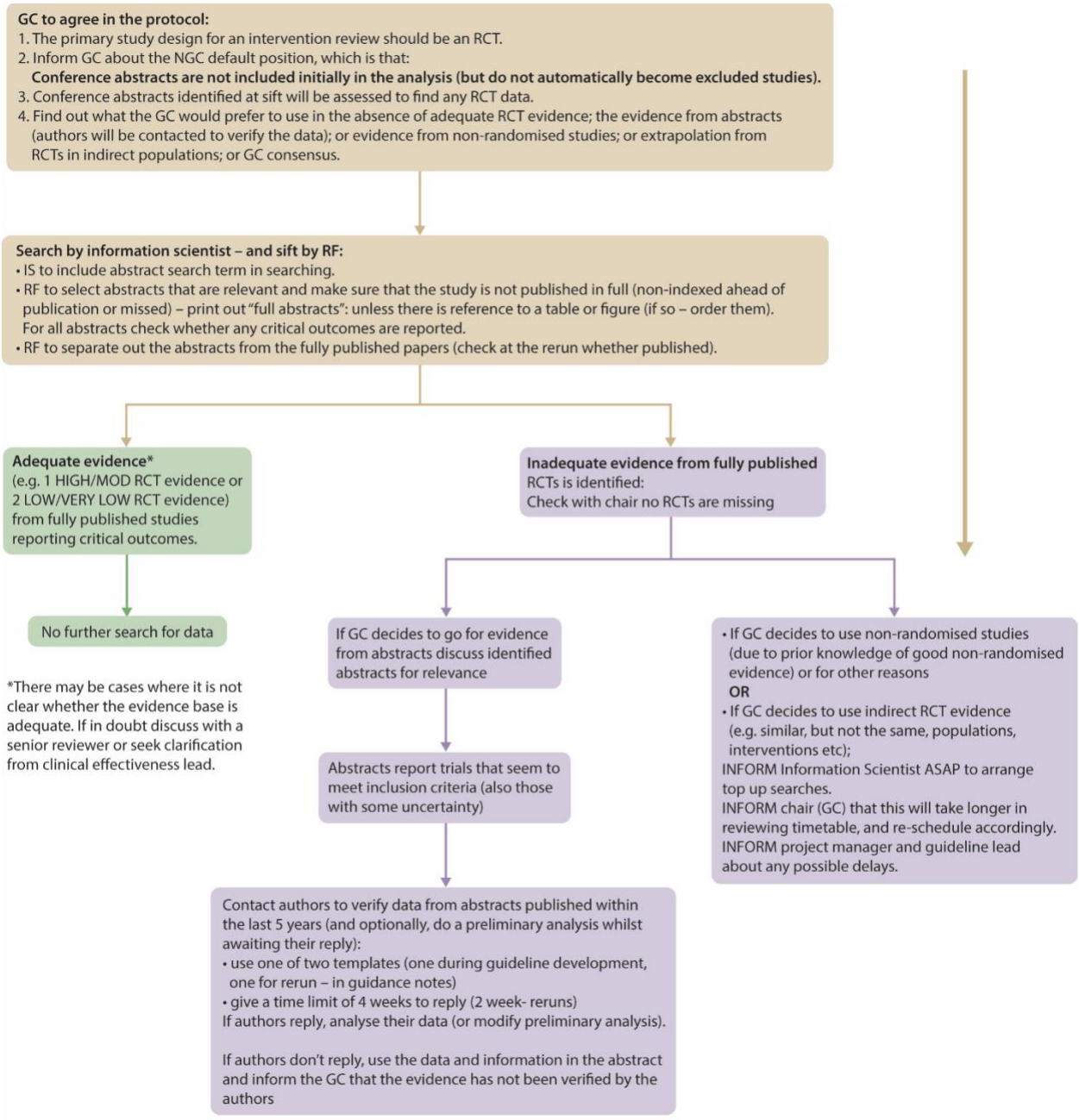
Use of existing systematic reviews are also appropriate to include for each of the review types and could be considered as a study design to include as standard in all review protocols.

Further details related to the study design should also be considered within the protocol. For intervention reviews, for example, the “unit of analysis” within the study may also be important to specify. Within studies, the most common unit of randomization is at the individual level. However, study investigators may also randomize interventions to groups of people (“clusters”) or parts of patients (e.g., hands, lesions). Furthermore, individual patients may receive more than one intervention, but in a random order (“crossover trials”).

Study designs such as crossover trials are not always appropriate – for example, if the natural course of the patient’s condition changes with time (i.e., progressive or regressive conditions) or if the interventions result in a permanent change in an outcome (“cure”). The appropriateness of these to the review question should be considered by the WG when setting the protocol. Where RCTs are included, a statement should also be made about whether crossover trials can be included and, if so, whether a minimum washout period is required between crossover periods.

A commonly recognized hierarchy of studies has been suggested (Figure 2). For intervention reviews, where it is likely that there will be insufficient RCTs to inform decision making, the WG should consider what level of evidence (in terms of study design) they will consider appropriate to include (and will enable a recommendation to be made) before relying on expert consensus opinion. It is noted that it is likely in many reviews that RCTs alone will not answer the questions for this area of research. Discarding lower levels of evidence *a priori* due to methodological quality alone is not considered an appropriate option without a clear rationale. The certainty of the evidence is taken into account in the GRADE assessment and is subsequently reflected in the strength of the recommendations.

Figure 2. National Guideline Clearinghouse (NGC) conference abstract process



ASAP, as soon as possible; GC, guideline committee; IS, information scientist; MOD, moderate; RCT, randomized controlled trial; RF, research facilitators

Any decisions on levels of evidence deemed appropriate to include (or exclude) should be stated in the protocol. For example, there may be occasions where the WG agrees that higher quality indirect evidence would be more informative than cross-sectional studies or case series/reports. If so, the type of indirectness that will be acceptable should be stated (e.g., using evidence from an adult population to inform recommendations for children). It is important that all decisions regarding the types of evidence that are used are centered around what evidence will enable a recommendation to be made.

For reviews of diagnostic accuracy, diagnostic RCTs or “test and treat” trials can also be considered. In some cases, RCTs are considered the best study design to determine the best diagnostic tool as they enable assessment of the effect of the diagnostic method on important patient outcomes. However, they are infrequently available in the literature. WGs are therefore advised when considering reviews of diagnostic accuracy to consider these alongside a more traditional review of diagnostic accuracy from cohort studies. Again, within diagnostic accuracy reviews, it is important to consider whether a lower level of evidence will add to the ability to make a recommendation before proceeding with additional analysis.

When searches are expanded to cover a range of study designs, the volume of abstracts to sift through can be greatly increased. It is important to ensure that this additional work in sifting and analyzing data will add value to enabling recommendations to be made. Some pragmatic options to help focus workload are suggested:

- Apply search filters to separate RCTs from non-randomized studies so that these can be sifted separately.
- Tag records when filtering according to level of evidence so they can easily be separated out and viewed in a stepwise fashion. For example, a search of non-randomized studies will include both comparative and non-comparative studies, as well as case control and cross-sectional studies. It may not be appropriate to include all of these in the analysis, and therefore potentially relevant cross-sectional studies (for example) can be tagged but not analyzed until a later stage if required, but they will now be easily identified in the search.
- Analyze levels of evidence by their hierarchy rather than by author or any other order. This enables a decision to be made on whether evidence is sufficient before undertaking unnecessary work.
- Set up regular touch points between the WG and ERT to review progress so far. For example, after each level of evidence suggested in the hierarchy has been considered to determine:
    - Whether the level of available evidence is sufficient to base recommendations on. [Note: This should include consideration of the sample size and quality of the individual studies, not just the number of studies.]
        - What should the next step be? Move to lower-level evidence in the hierarchy, indirect evidence, or consensus? [Note: Always consider what will best enable a recommendation to be made.]
    - How should the data be meta-analyzed (if appropriate)? For example, will different levels of evidence be pooled?

Select and rank outcomes

The WG, in collaboration with the ERT, develops a list of relevant outcomes that will be considered for each PICOS question. The focus should be on patient-important benefits and harms. Outcomes should be clearly defined (including clarification of their measurement and timeframe), particularly when there may be multiple ways of reporting or interpretation. For

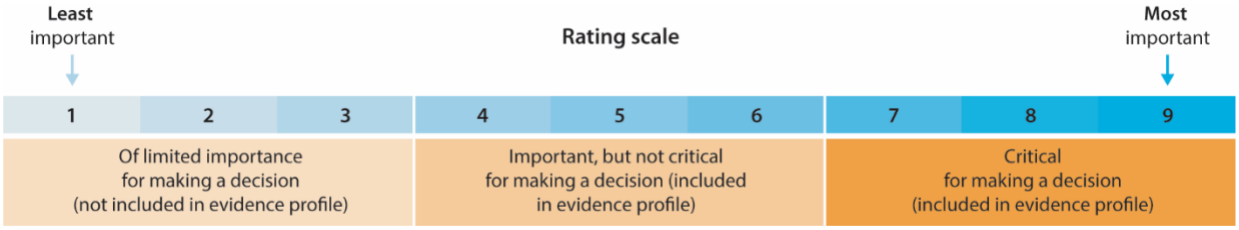
example, key comorbidities should be defined, and instruments used to assess “health-related quality of life” should be specified.

To achieve that, we suggest the following strategies:

- The ERT provides a list of outcomes that have been measured in studies.
- WG members should list any other outcomes that have not been reported in studies but are important for decision making.
- It is essential to include both benefits and adverse effects in the outcome list.

Members of the WG independently rank the benefits and harms according to GRADE methods.[21] Three categories of outcomes are considered based on their importance for decision-making: 1) critical, 2) important (but not critical), and 3) not important. The initial GRADE rankings range from 1 to 9, with 1 being not important for decision-making and 9 being of most critical/important for decision-making (Figure 3). WG members can use the same rating several times (i.e., same number for ≥1 outcome). This could be achieved by a WG member survey.

Figure 3. Likert scale for ranking the importance of outcomes



Outcomes ranked from 7 to 9 are critical for decision-making, those ranked from 4 to 6 are important but not critical, and those ranked from 1 to 3 are not important. Only outcomes and harms considered important (rating 4–6) or critical (rating 7–9) are included in the EvP/SoF tables. Only outcomes considered critical (rating 7–9) are primary factors influencing a recommendation; these are used to determine the overall certainty of evidence supporting the recommendation.

Factors to consider when ranking outcomes and harms include:

- Rankings are judgements about the values and preferences of patients and families.
- KDIGO attempts to focus on outcomes that it believes will be important for clinicians to discuss or highlight with a patient when presenting the potential benefits and harms of a preventive service.
- The judgments are relative, not absolute (i.e., weighing the importance of each outcome in relation to other relevant outcomes for the specific decision that is being considered).
- Surrogate outcomes are important only to the extent that they reliably indicate directly to important outcomes, where important outcomes have not been measured and reported in studies.

A summary of “mean importance” should be discussed with the panel. A discussion may be needed to address outcomes with a wide range of importance and considerable variability in rating among panel members. The WG discusses the rankings and comes to a consensus about overall assessments of outcomes as critical, important, or less important.

Critical benefits and harms are of decisive importance, indispensable, and likely to determine a decision about care. They should be included in the SoF tables and are considered when determining the overall certainty of evidence. Important outcomes are meaningful, consequential, and may influence a decision. They will usually be included in the SoF tables, but their inclusion may depend on the total number of important outcomes. The overall certainty of the evidence is not influenced by important outcomes. Outcomes of no importance are not included in the SoF tables and are not considered when determining the overall certainty of the evidence.

Clinically relevant outcomes are strongly preferred, but WGs may consider the use of validated surrogate outcomes if trial evidence about clinically relevant outcomes (e.g., mortality) is lacking. Relying on a surrogate outcome (especially a putative or unvalidated surrogate) would result in downgrading the certainty of evidence. If there is insufficient trial evidence for clinically relevant outcomes, surrogate outcomes that meet the following criteria may be considered:

- A high proportion of people with the surrogate outcome are expected to experience the condition or the outcome.
- Intervention directed toward the surrogate outcome leads to improvements in the clinically relevant outcome.
- Intervention directed toward the surrogate outcome results in a net benefit (e.g., benefits should outweigh harms).
- The validation is based on multiple studies.

It is ideal to develop a list of outcomes per PICO. However, often multiple PICOs in the same guideline may be related, and the panel could prioritize outcomes for a group of related PICOs simultaneously. It is important to complete the outcome prioritization even when there is sparse evidence. The results of the outcome prioritization can help identify evidence gaps and inform future research recommendations. While most outcomes have some importance, it can be difficult to consider all outcomes when making the final recommendation. Therefore, evidence will be gathered for important and critical outcomes and will be considered when making the final recommendation

Collect patient input in the selection and ranking of outcomes

Where relevant, the work of patient-centered organizations should be reviewed when ranking the importance of outcomes. An example of this type of work is the core outcomes sets developed by the Standardised Outcomes in Nephrology (SONG) project.

In addition to defining the clinical questions, the evidence review protocol(s) should outline the methods for:

- Development of Search procedure
- Study selection and Data extraction
- Grading the risk of bias for outcomes of individual studies
- Evidence synthesis
- Development of SR deliverables (Preparation of summary tables and evidence profiles)
- Plan for delivery of all ERT deliverables

Statistical analysis plan

A statistical analysis plan (SAP) should be provided to the WG for review and approval prior to quantitative evidence synthesis.

Characteristics of included studies

A starting point for synthesis is to summarize the PICOS characteristics of each study (i.e., the PICOS of the included studies) and categorize these PICOS elements in the groups (or domains) pre-specified in the protocol (i.e., the PICOS for each synthesis). The resulting descriptions are reported in the “Characteristics of included studies” table and are used to determine which studies can be grouped for synthesis.

Summary of analyses to be conducted

The SAP outlines the methods for conducting the appropriate meta-analyses based on recommendations in the assessment of study characteristics. In addition to presenting the specific methods and outcomes that will be analyzed, the SAP characterizes the outcome measures, definitions, and timepoints that will be used in base-case analyses (analysis of all eligible studies). If applicable, the SAP should outline and define appropriate subgroup and sensitivity analyses to document relevant variations in statistical methods or inclusion criteria compared with the base-case analyses. Sensitivity analyses may include an adjustment for covariates or scenario analyses (used to test the robustness of data by running analyses with and without extreme cases included).

The SAP should also briefly describe how all results will be presented, including any applicable descriptive statistics (e.g., relative and absolute measures of effect), tables of studies used for each outcome, and tabular and graphical representations of results from the quantitative analyses.

Lastly, the SAP should provide an estimated timeline for the delivery of results to the WG. A teleconference may be scheduled with each writing group for the presentation of findings by the ERT.

Document the timeline for evidence reviews

The timeline for each deliverable should be included in the protocols. The deliverables include the final protocol, screening results, summary tables with risk of bias (RoB) assessment for each study by study design, EvP/SoF tables with GRADE assessment across all studies, statistical analysis plan, analysis findings, the draft evidence review(s), the final evidence review(s). The KDIGO team, the ERT Director, and the Guideline Co-Chairs review and approve the proposed timelines.

WG review of evidence review protocols

Once the penultimate draft protocol from the ERT is complete, KDIGO will circulate the draft to all WG members. Members will have approximately two weeks to review the protocol draft and provide feedback. KDIGO will compile WG feedback into a single document to be shared with the ERT.

Conduct preliminary search

After a guideline topic has been selected, the ERT scans the literature and provides the WG Co-Chairs with a list of relevant studies. The scan should not be exhaustive and should not address potential review questions in detail. The goal is to provide an overview of the topic and to identify potential challenges with the evidence. The scan will initially concentrate on existing guidance and systematic reviews; if no relevant existing guidelines or systematic reviews are identified, a search for primary studies is conducted.

Prepare results and develop a topic refinement document

The ERT summarizes the evidence found in the scan and identifies the articles that WG members should skim or read. The summary includes an explicit description of any relevant guidance (scope, clinical questions, target population). If relevant, new evidence since prior guidance was developed is highlighted, as are changes in clinical practice that may necessitate new clinical questions or changes to existing questions.

Interactions between Work Group and Evidence Review Team

The output from the preliminary search is provided to the WG with at least two weeks' notice, and ideally with an opportunity for the WG to give feedback on the content of the output, and/or to ask for additional relevant material to be added. Ideally, a call is scheduled between the WG and the ERT, allowing the WG to ask questions, identify any gaps, and discuss the direction of the guideline. The ERT prepares a summary of this discussion, focusing on elements related to the clinical questions, the PICOS terms, and the inclusion/exclusion criteria that will be used in the searches for the systematic reviews.

Meeting Zero

The goal of the meeting is to finalize the protocol derived from the Scope of Work prior to the formal evidence review process. The meeting is attended by the KDIGO Co-Chairs (1 or both), WG Co-Chairs, ERT, Methods Committee representative, and KDIGO team.

As this is the first in-person meeting between the WG Co-Chairs and ERT, the ERT will first provide an overview of their process. They will then discuss the yield from the scoping exercise and proposed refinement of key clinical questions and/or their PICOS criteria.

All attendees will then discuss the refinements to the protocol and any accompanying analytic frameworks. The group will also discuss and finalize the logistics of the process (key steps, timeline, meetings, communication) and outline the vision for final work products (list of and format for deliverables, graphical presentations, knowledge translation or implementation tools, and process for review of deliverables).

Once the draft protocol has been revised by the ERT based on the feedback from Meeting Zero, the protocol will then be shared with the WG for final comment and approval before it is finalized. This protocol revision process should take approximately two weeks, and the WG should be given an additional two weeks for review.

When the final protocol is approved, it will be shared with the KDIGO team for posting to the KDIGO website. The ERT will also register the protocol in the International Prospective Register of Systematic Reviews, also known as PROSPERO.

The ERT logs decisions that affect the protocols as the project evolves and updates the protocol. Revised versions are dated and labeled with a modification number, and the PROSPERO registration file is updated accordingly. The ERT notifies the WG of any protocol revisions that have implications for their work. At the time of the final guideline publication, the ERT sends the final protocol (including any amendments) to KDIGO for posting on the KDIGO website.

The final protocol will also be shared with the KDIGO KT lead, who will review the clinical questions and consider possible KT-related issues that may arise with the dissemination of the guidance.

Conduct the evidence reviews

Overview

The overall process for conducting the evidence review and developing KDIGO clinical practice guidelines should adhere to the National Academy of Medicine (formerly the Institute of Medicine (IOM)) Standards for systematic reviews and guideline development.[22, 23] The

guideline should be conducted and reported in accordance with the AGREE II reporting checklist (Appendix C. Checklists to assess the quality of the methodological process for systematic review and guideline development).[24]

Evidence review completion is the responsibility of the ERT. The evidence review process includes the following steps [Note: The steps in **bold** below are essential "check-in" points for the WG and ERT to communicate]:

- Search strategy development: This is the responsibility of the ERT. However, the WG could provide input including:
    - **Early identification of 'seed' articles**: After finalizing the list of PICOs to be addressed as formal recommendations, the WG should provide example articles that will inform these PICOS. This is not meant to be an exhaustive list; it is rather a list of examples that could be useful in developing search strategies to initiate the evidence review.
    - The WG should also indicate which PICOS questions are expected to have no direct or very sparse evidence. This will facilitate early discussion around the need to identify additional indirect evidence and may have implications on the inclusion and exclusion of certain articles.
- Initial search results: Giving the sparsity of the evidence in many areas in nephrology, we suggest that the initial search strategy is not limited to any study design.
- Title and abstract screening: The ERT may implement a process of triaging and prioritizing evidence based on high-quality evidence rather than excluding certain study designs. For example, the ERT may start with evidence from randomized trials and, if that does not exist, identify evidence from comparative observational studies and if that does not exist, identify evidence from non-comparative studies, etc. This triaging process could help flag low-quality evidence and indirect evidence to be used only if high-quality evidence is lacking. This could also improve efficacy and avoid the need for additional searches later in the process.
- Full text screening results and evidence mapping: The ERT will start screening articles that are considered relevant.
- **Summary of list of articles per PICOS question and excluded studies**: After full text screening is complete, the ERT should provide a list of studies, which will inform each PICO, and a list of excluded studies with brief reasoning for exclusion.
- **Evidence map**: It is important that the ERT provides a high-level evidence map to the WG at this stage. The evidence map will stipulate an overview of the landscape of the evidence per PICOS.
- **Discussion about the available evidence**: It is important that the ERT and WG have an explicit discussion about the available evidence, or lack thereof, and plan moving forward for PICOS with sparse or "no" evidence. This check-in point provides an opportunity to identify any additional evidence that is informative for specific recommendations. It will also facilitate early discussion around the need to assess indirect evidence.
- Data extraction: The ERT should complete data extraction of data that will inform decisions about the effectiveness of certain management strategies (e.g., interventions

or tests) and the quality of the evidence, including the directness of the results. To facilitate an effective process, the ERT should consult with the WG and share data tables to inform extraction forms. It will be helpful if the WG Co-Chairs and chapter leads provide input on the essential data point which could influence final decisions.

- **Results**: Early draft of results will include a summary of included studies (preferably in the form of a table; see example Table 8). This summary should include information about the study, PICOS elements, and RoB assessment.
- **Final GRADE EvP/SoF tables**

Table 8. Example of summary table

Study	Population	Intervention	Comparison	Outcomes reported	RoB
Study 1: Author, year					
Study 2: Author, year					

RoB, risk of bias

Search procedure

The ERT will develop search strategies based on the final scope for the evidence reviews and eligibility criteria (PICOS). Search strategies should be developed with a medical librarian experienced in systematic review. Search strategies should be further peer reviewed by a second experienced medical librarian not in the ERT. It is acceptable, and in many cases preferable, to split the searches into modules by topic or domain.

Electronic searches should be conducted using terms relevant to the guideline. Depending on the database, search terms should include MeSH or Emtree terms[2] (or equivalent) and also free-text words. It is common and acceptable to develop the primary search in Medline or Embase and to translate these into other databases. Established, peer-reviewed filters should be used in preference over *ad hoc*, topic- or ERT-specific filters[3]. The current best source for such a filter is the InterTASC Information Specialists' Sub-Group (ISSG).[4]

Search strategies should be adapted to the language of each database listed below but will maintain the same search terms. With rare exceptions (approved by the WG Chairs and the Methods Committee representative), searches should not include any language or geographic restrictions. Publication date restrictions should be applied only if a justifiable case can be made

[2] MeSH = Medical Subject Headings (in PubMed), Emtree = Embase subject headings.
[3] Filters are sections of the search designed to exclude (or focus on) sets of citations such as non-primary studies, non-human studies, only comparative studies
[4] https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home

for why older studies are not applicable. This logic will need to be fully described in the protocols and the Methods Chapter of the guideline.

Care should be taken to avoid over-filtering (inadvertently deleting eligible studies in bulk) or attempting to overly increase specificity (reducing total number by minimizing off-topic citations) at the expense of sensitivity (ensuring that all eligible studies are found).

- One example is ensuring the use of the "NOT-NOT" concept: If excluding studies of children, do not simply use "NOT children" but instead use "NOT (children NOT adults)" so that studies of children and adults are not excluded.
- Another example is using overly focused search terms (e.g., omitting the class of drug when listing specific drugs to search for, insufficiently including synonyms and related concepts).
- Another example is adding multiple "AND" operators with the goal of reducing citation volume. All "AND" operators should be double-checked to ensure they should not be "OR" operators.

It is important to note that all final search strategies will be published in the Data Supplement to the final guideline.

As part of the search process, it is recommended that existing systematic reviews and other clinical practice guidelines be included, and then be reviewed for possible inclusion (as evidence sources) or as a reference in terms of their bibliography, or both. The search should also include a search of major clinical registries to identify trials that have ended recently or are likely to report while the guideline is being developed.

The WG members should be solicited multiple times to suggest other studies that may meet eligibility criteria. The public review step is another possible source of eligible studies. Regardless of their source, all studies should meet the final study eligibility criteria for inclusion in systematic review.

New guideline versus guideline update

The search procedure for *de novo* guidelines and guideline updates should be the same in terms of the steps outlined in the following sections. When conducting literature search updates for a formal guideline update, all searches from the original guideline systematic review should be carefully reviewed to ensure relevance and current accuracy and validity. Any searches that are maintained without change for the update should be run with an overlap of 6-12 months with the last search run for the original guideline. If any new search terms or concepts are added to the original search, focused searches with these new terms should be run without date restriction. The goal is to ensure that older studies that meet the newer search criteria are not omitted because they hadn't been searched for with the original review.

Sources

Electronic database searches

At a minimum, searches should be conducted in Medline (e.g., via PubMed or Ovid), Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews (CDSR). The following electronic databases should be searched for both the *de novo* guidelines and guideline update:

- Embase
- Medline and Medline In-Process
- The Cochrane Library (both CENTRAL and CDSR)

Depending on the topic and scope of the review, additional databases should be considered for possible inclusion. Examples include CINAHL, LILACS, PsycInfo, and SocINDEX. Further consideration should be made regarding searches in ClinicalTrials.gov, the EU Clinical Trials Register, UMIN Clinical Trials Registry (UMIN-CTR), the Japan Medical Association Center for Clinical Trials (JMACCT), and other study registries.

Hand-searches

Grey literature searches should be conducted to identify recent relevant research that may not have been published in peer-reviewed journals and, thus, were not captured by the database searches.

If the ERT and WG Co-Chairs determine that recent conference abstracts should be included, they should develop a complete list of conferences and/or professional organizations of interest. Available published conference abstracts (including posters and oral presentations) should be hand-screened. Typically (and acceptably), only conferences within the prior 2-3 years are included.

These abstracts should help indicate recent studies that may be published during the course of the guideline development process. They should not be eligible for inclusions in evidence synthesis for a guideline as the publications are not peer-reviewed, and results are likely to change between the abstract and final publication. Once full-text studies are available, the studies may be included in the evidence review.

Search validation

Once finalized, the search algorithm should be validated by a second independent reviewer to confirm there are no errors. When available, the search results should be cross-checked against the bibliographies of the most recently published, relevant systematic reviews (i.e., published in the last two years) identified via the database searches. The systematic reviews themselves will not be included in the review to avoid double-counting of relevant studies. In the case of the guideline update, the cross-referencing should include studies previously identified for the prior version of the guideline.

Study selection

The study selection process will involve evaluating records retrieved by the searches against the final PICOS criteria to establish which studies are suitable for inclusion. Ultimately, none of the exclusion criteria and all of the inclusion criteria should be met for a study to be selected for inclusion in the reviews. Should additional selection criteria be applied during either screening level, this protocol should be amended accordingly.

Title and abstract screening

The corpus of searched citations should be independently screened in duplicate. It is recommended that at the initiation of citation screening, all screeners (including the ERT Director) should screen collections of randomly selected citations (e.g., a collection of 100 citations). The ERT should, as a group, review all conflicts with the goal of ensuring that all team members understand the study eligibility criteria. This “pilot round” screening may need to be repeated several times until the ERT is sufficiently confident that there is consensus about the eligibility criteria.

Each title and abstract should be reviewed by two independent investigators to determine its suitability for inclusion in the systematic review according to the inclusion/exclusion criteria defined in the PICOS framework. Discrepancies should be resolved by a third investigator. An alternative that some ERTs may prefer is to accept all citations that have been accepted by any team member (i.e., to move all conflicts to the next screening stage). However, this approach may greatly increase the number of full-text articles that need to be retrieved and re-screened.

Again, abstracts must meet none of the exclusion criteria and all protocol-specified inclusion criteria to pass this level. No study should be excluded at the title and abstract level solely because it provides insufficient outcome information.

It is recommended that citation screening software is used that allows independent screening by multiple users and has a mechanism to resolve conflicts. There is no requirement to use any particular software or process as long as double, independent screening occurs with a process for conflict resolution. Ideally, the software should have machine learning capabilities to improve the efficiency and accuracy of citation screening. Examples are included in the footnote; however, this is not a definitive list.[5] The available software is constantly changing and evolving. Some software provides the potential to stop screening (or at least stop double-screening) when

[5] abstrackr (http://abstrackr.cebm.brown.edu/)
ASReview (https://asreview.nl/)
Covidence (https://www.covidence.org/)
DistillerSR (https://www.evidencepartners.com/products/distillersr-systematic-review-software)
PICO Portal (https://picoportal.org/)
rayyan (https://www.rayyan.ai/)
Research Screener (https://researchscreener.com/)
RobotAnalyst (http://www.nactem.ac.uk/robotanalyst/)
SWIFT-Active Screener (https://www.sciome.com/swift-activescreener/)

a certain threshold has been met. However, no software has yet demonstrated adequate validity of any stopping rule that would apply to all literature searches.

Full-text screening

For abstracts that are deemed relevant during title and abstract screening, the corresponding full-text articles should be retrieved for further screening. Each full-text paper should be reviewed by two independent investigators. Discrepancies should be resolved by a third investigator as necessary. For each excluded study, a specific reason for the exclusion should be provided in the study listing.

During the screening process, key information should be captured to gain additional visibility into the available evidence for each systematic review topic. These characteristics may be used to prioritize full-text screening of select studies or to apply more stringent selection criteria if the inclusion rate exceeds the scoped number of articles. Collection of this type of data would be efficient for the development of evidence maps.

Study listing

Once the screening is completed, the study attrition through both abstract and full-text screening should be mapped using PRISMA flow diagrams. If relevant studies are identified through other sources or through search validation, these studies should be documented transparently in the PRISMA diagram to follow the evidence review's systematic approach.

A study listing (in Microsoft Excel® format) of accepted primary studies (and their related publications or reports); articles excluded at full-text screening, organized by reasons for exclusion; and the full list of all studies screened at the abstract or full-text level should be provided to the WG.

Depending on the scope of the evidence reviews and the normal working routines of the ERT, the team may choose to develop an "evidence map." The evidence map may be initiated at the abstract or the full-text level. The concept is to extract simple information about each study into a simple database. Some of the listed software programs enable this step to be conducted during abstract screening. Possible items to be extracted are topic/subtopic addressed, study design, sample size, population category, and intervention(s). Only as much information as is needed to enable decision-making about the systematic review or determining which citations to retrieve in full text (or to move on to the next phase of screening).

For inclusion in the guideline Data Supplement, the ERT should create a table to summarize the flow of literature for each systematically reviewed topic. The table should include each guideline chapter (and, as relevant, sub-chapter), each topic, key questions, PICOS criteria within the systematic review in a separate row, and whether summary tables and evidence profiles are included for each topic.

Use of existing systematic reviews

The use of existing systematic reviews in the development of KDIGO guidelines is encouraged. These reviews can be useful for the development of search strategies, review of reference lists, and efficiencies in the evidence review, among other tasks.

If an existing systematic review from another organization is to be used to replace a *de novo* review by the ERT for the purpose of a KDIGO guideline, it should first be assessed for methodological quality by the ERT using the AMSTAR 2 checklist. The ERT should also ensure the key questions addressed by the systematic review align with the key questions from the guideline.

Data extraction

Once the list of included studies has been finalized, the ERT should design a data extraction template (DET) based on the data elements listed in the approved evidence review protocols. Examples of data elements that may be captured from studies include design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, predictors, outcomes, and results. The study methodology and outcomes should also be assessed for risk of bias (see Grading the risk of bias for outcomes of individual studies).

Two general approaches are acceptable for data extraction: 1) Full data extraction of each study by two ERT members done independently, with a formal process for reconciliation of conflicts; or 2) Full data extraction by a single ERT member with complete review and correction by a second, independent ERT member, with a formal process for reconciliation of non-trivial corrections. Other, or hybrid, approaches are also acceptable, as long as at least two ERT members enter or confirm each data item within each extraction, with formal processes for reconciliation. At least one of the extractors for each study should be a more senior or experienced member of the ERT.

Preparation of summary tables and evidence profiles

Development of summary tables

Once the data are extracted, summary tables should be developed for each review topic summarizing the results of the evidence review. Summary tables typically contain outcomes of interest, relevant population characteristics, description of intervention and comparator (or predictor), results, and quality grading for each outcome. Categorical outcomes and continuous outcomes should be tabulated separately. The exact details of the summary tables (e.g., format, elements for extraction, software, etc.) are left to the discretion of the ERT; however, the table shells should be shared with the WG prior to development. WG members review and confirm all summary table data and quality assessments. This should be done before any evidence synthesis is conducted. Summary tables should be made available on the KDIGO website.

Evidence synthesis

Most commonly, this is the statistical combination of results from two or more separate studies (henceforth referred to as meta-analysis) of effect estimates.

- Synthesis is a process of bringing together data from a set of included studies with the aim of drawing conclusions about a body of evidence. This will include synthesis of study characteristics and, potentially, statistical synthesis of study findings.
- A general framework for synthesis can be used to guide the process of planning the comparisons, preparing for synthesis, undertaking the synthesis, and interpreting and describing the results.
- Tabulation of study characteristics aids the examination and comparison of PICOS elements across studies, facilitates synthesis of these characteristics and grouping of studies for statistical synthesis.
- Tabulation of extracted data from studies allows assessment of the number of studies contributing to a particular meta-analysis, and helps determine what other statistical synthesis methods might be used if meta-analysis is not possible.[25]

An examination of the included studies always precedes statistical synthesis. More broadly, synthesis of the PICOS elements of the included studies underpins the interpretation of review findings and is an important output of the review in its own right. This synthesis should encompass the characteristics of the interventions and comparators in included studies, the populations and settings in which the interventions were evaluated, the outcomes assessed, and the strengths and weaknesses of the body of evidence.

Conduct evidence synthesis

Once extracted, the relevant data should be synthesized according to the SAP. The appropriate method for synthesizing data will depend on the type of review question and outcome data as defined in the PICOS. Wherever possible, data should be pooled to provide a summary statistic and its variability to provide a better estimation of the effect than results from a single study, referred to as meta-analysis. Guidance on appropriate methods of meta-analysis should be followed, for example, the Cochrane Handbook for Systematic Reviews.[26]

It is expected that both the relative and absolute effects and their variability (for example, with a 95% CI or SD) should be displayed for the outcomes of interest, irrespective of whether or not meta-analysis has been carried out. Relative effects may be risk ratios, odds ratios, or hazard ratios, as appropriate. Mean differences or standardized mean differences should be presented for continuous outcomes.

The certainty of the evidence should be considered, including RoB, assessment of heterogeneity, imprecision in the effect estimates, and assessment of reporting biases. These can be considered using the GRADE approach, and both the effect estimates and certainty rating can be presented in GRADE profiles.

Graphical displays of results can be used to illustrate the effects and their confidence intervals, for example, forest plots. These can also be used whether or not meta-analysis has been possible.

Minimum expectations of evidence synthesis

- Evidence synthesis should be consistent with the protocol and SAP
- Where possible, data should be pooled in a meta-analysis
- Relative effects with a measure of variance should be presented as well as absolute effects
- The certainty of this evidence should be assessed (preferably using the GRADE approach where relevant) irrespective of whether meta-analysis has been undertaken
- Outputs of the analysis and certainty rating should be reported per outcome, preferably in GRADE profiles

Figure 4 provides a general framework for evidence synthesis that can be applied irrespective of the methods used to synthesize results. The sections of the SAP are discussed in more detail below.

Figure 4. General framework for evidence synthesis

Stage 1. At protocol stage:	
Step 1.1	Set up the comparisons.
Stage 2. Summarizing the included studies and preparing for synthesis:	
Step 2.1	Summarize the characteristics of each study in a "Characteristics of included studies" table, including examining the interventions to itemize their content and other characteristics.
Step 2.2	Determine which studies are similar enough to be grouped within each comparison by comparing the characteristics across studies (e.g., in a matrix).
Step 2.3	Determine what data are available for synthesis.
Step 2.4	Determine if modification to the planned comparisons or outcomes is necessary, or new comparisons are needed, noting any deviations from the protocol plans.
Step 2.5	Synthesize the characteristics of the studies contributing to each comparison.
Stage 3. The synthesis itself:	
Step 3.1	Perform a statistical synthesis (if appropriate), or provide structured reporting of the effects.
Step 3.2	Interpret and describe the results, including consideration of the direction of effect, size of the effect, certainty of the evidence, and the interventions tested and the populations in which they were tested.

Once evidence synthesis is complete, the ERT should incorporate the findings into the existing summary tables and evidence profiles. This can include both absolute and relative effect estimates, CIs, and any other information deemed relevant for decision-making.

Evidence profiles/Summary of findings tables

Evidence profiles (EvP)/Summary of findings (SoF) tables are constructed to assess and record certainty grades and descriptions of effect (or association) for each outcome across studies, as well as the certainty of overall evidence and description of net benefits or harms of the intervention or comparator across all outcomes. These tables aim to make the evidence synthesis process transparent. Decisions in the EvP/SoF tables are based on data from the primary studies listed in corresponding summary tables and on judgments of the ERT and WG. Each EvP/SoF is initially constructed by the ERT and then reviewed, edited, and confirmed by the WG and/or WG Co-Chairs.

A well-formatted EvP/SoF includes the following:

- Each row provides a summary for an outcome (not per outcome measure)
- It may be appropriate to use EvP/SoF for multicomparison interventions
- It is appropriate for evidence synthesis per outcome to be based on the results of one study or to be only qualitatively summarized
- At least one EvP/SoF per recommendation is expected
- The EvP/SoF should include relative and absolute effects (ERT can assume baseline risk based on identified studies and confirm with the WG Chairs or Chapter leads
- The ERT should provide their assessment of certainty of evidence which could be changed by panel as needed
- The ERT should provide an overall summary of the *Certainty of evidence* for each recommendation
- The ERT should provide a list of references that could facilitate referencing the guideline document once ready

Grading the certainty of evidence

Grading the risk of bias for outcomes of individual studies

As part of data extraction, each study must be assessed for potential RoB and/or methodological quality (or limitations). As for data extraction, this should be conducted either fully independently or singly with a second review, either way with a formal process for conflict resolution.

KDIGO does not require the use of specific RoB assessment tools. The ERT should acknowledge and use the most appropriate RoB tool for the study design being evaluated. However, approaches other than the suggested ones must be discussed and confirmed with the WG Co-Chairs, KDIGO team, and Methods Committee representative (Table 9). Even within the

context of using the suggested tools, the Methods Committee representative should sign off on the specific risk of bias/methodological questions to be implemented. The chosen tools should be used consistently throughout the evidence review of the guideline.

It is also important to note that the same study may inform different PICO questions in a different way and may require different RoB assessments. For example, RCT trials may provide direct evidence for one PICO question and indirect evidence for another PICO question, which may necessitate different RoB assessments.

For randomized controlled trials, the ERT should use either the original Cochrane RoB tool or the Cochrane RoB.2 tool.[27] For observational studies of interventions (either comparative or single group), the ERT should use the relevant questions from ROBINS-I.[6] The ERT, with input from the Methods Committee representative, should exercise judgment regarding the detail to which the tools are implemented. KDIGO recognizes that not all topics (and studies) require rigorous implementation of all aspects of RoB assessment as described by the more complex assessment tools (e.g., ROB.2 and ROBINS-I).

Table 9. Acceptable tools for grading the risk of bias of individual studies

Study design	Accepted tools
RCTs	Cochrane RoB 1 Cochrane RoB 2
Non-randomized comparative studies	GRACE ROBINS-I SIGN Methodology Checklist 3
Prospective cohort studies	ROBINS-I
Retrospective cohort studies	
Systematic reviews	ROBIS
Diagnostic test studies	QUADAS
Harms	[use the same RoB tool based on study design as above]

GRACE, Good ReseArch for Comparative Effectiveness; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; RoB, risk of bias; ROBINS-I, Risk Of Bias In Non-Randomized Studies – of Interventions; ROBIS, Risk of Bias in Systematic Reviews; SIGN, Scottish Intercollegiate Guidelines Network

Where appropriate, studies should be assessed for RoB for each extracted outcome. Examples include situations where the numbers analyzed (or dropout rates) differ across outcomes, where only some outcomes are adjusted for potential confounders, or where the definitions of specific

[6] Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I). https://sites.google.com/site/riskofbiastool/welcome/home?authuser=0

outcomes are unclear or problematic. Note that assessment tools or reporting checklists (such as QUADAS-2, CONSORT) should not replace RoB assessment.

Each reported outcome should then be evaluated and given an individual rating depending on the certainty of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome cannot exceed the quality grade for the overall study.

Grading the certainty of evidence across outcomes

To avoid confusion between the “Quality of evidence” and “quality of studies” (or RoB), GRADE recently changed its terminology from “Quality” to “Certainty” of evidence. For grading purposes, “quality” and “certainty” relate to the same thing, and GRADE allows each group to choose which term is best suited to their guidelines. Since 2022, KDIGO has decided to adopt the term “Certainty of evidence” to make a distinction between the assessment of individual studies and the assessment of the evidence base across outcomes. The “Certainty of evidence” refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation (Table 10).

Table 10. Final grade for overall certainty of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

A structured approach, based on GRADE and facilitated by the use of EvP/SoF tables, should be used to grade the certainty of the overall evidence for each outcome across studies. For each topic, the discussion on grading the certainty of the evidence is led by the ERT.

Grading the certainty of evidence for each outcome across studies

Following GRADE, the certainty of evidence pertaining to a particular outcome of interest is initially categorized based on study design (Table 11). For each outcome, the potential grade for the certainty of evidence for each intervention-outcome pair starts at high but may be lowered if there were serious limitations to the methodological quality (RoB) of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or a 95%

confidence interval (CI) spanning a range >1) or sparse (only 1 study or total N <500), or if there was thought to be a high likelihood of bias. The final grade for the certainty of the evidence for an intervention-outcome pair could be one of the following four grades: high, moderate, low, or very low (Table 10).

Table 11. GRADE system for grading certainty of evidence

Study design	Starting grade of certainty of evidence	Lower the grade	Raise the grade
Randomized trials	High Moderate	**Study limitations** –1, serious limitations –2, very serious limitations	***Strength of association*** +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
Observational study	Low Very low	**Consistency** –1, serious inconsistency –2, very serious inconsistency **Directness** –1, serious indirectness –2, very serious indirectness **Imprecision** –1, serious imprecision –2, very serious imprecision **Publication bias** –1, serious publication bias –2, very serious publication bias	**Other** +1 level if evidence of a dose–response gradient +1 level if all plausible confounding would reduce the demonstrated effect

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial

Grading the overall certainty of evidence

The certainty of the overall body of evidence is then determined on the basis of the certainty grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the certainty of overall evidence were A, B, C, or D (Table 10).

Assessment of the net health benefit across all important clinical outcomes

The net health benefit is determined based on the anticipated balance of benefits and harms across all clinically important outcomes (Table 12). The assessment of net benefit also involves the judgment of the Work Group and the ERT.

Table 12. Balance of benefits and harms

Strength	Level 1 for the intervention	Level 2 for the intervention	Neutral balance (Level 2 for either the intervention or the alternative)	Level 2 for the alternative	Level 1 for the alternative
Balance of EtD factors	Desirable effects clearly outweigh undesirable effects	Desirable effects probably outweigh undesirable effects	Trade-offs equally balanced or uncertain	Undesirable effects probably outweigh desirable effects	Undesirable effects clearly outweigh desirable effects

ERT deliverables

The following is a list of ERT deliverables from the evidence review:

- Detailed search strategy to be included as an appendix with the final guideline Data Supplement
- Report summarizing search results (e.g., PRISMA diagram)
- Study listing of screening results that includes a list of included and excluded studies with reasons for exclusion
- Evidence maps with an overview of the landscape of the evidence per PICO question.
- RoB assessment per study
- Summary tables of included studies
- GRADE evidence tables (EvP or SoF tables) for each PICO question

WG role in the evidence reviews

Once the guideline Scope of Work has been subjected to public review and finalized by the WG and ERT, the ERT will begin the initial steps of the evidence reviews. The WG will work with the ERT to draft the evidence review protocols, focusing on the key questions in the scope, defining PICOS, and ranking the importance of outcomes. This is aimed at limiting any downstream issues with “Scope creep.”

A common problem encountered in the development of guidelines is the tendency for the WG to expand the scope during various stages of guideline development. Sometimes, this is caused by “late-breaking” evidence. The reporting of the results of major trials affecting a guideline that is in development can usually be anticipated and incorporated in the evidence review and in the guideline. However, it can also happen that the WG wishes to alter or expand the original Scope of Work of the guideline because pertinent issues were overlooked when the scope was developed and subjected to public review. This often presents logistical problems in the evidence review process if, for example, altering or expanding one key question alters the search parameters of another already-completed key question search. Changing the scope and expanding the search parameters should be avoided whenever possible.

Format for writing the guideline

Guideline recommendations should be stated as clearly and concisely as possible to most accurately reflect what the WG wishes to communicate. This is usually best accomplished by following methods developed by KDIGO for writing guideline recommendations. Adhering to these rules for formulating guideline recommendations also allows users who are familiar with KDIGO guidelines to better understand what the WG wishes to communicate.

The WG is ultimately responsible for the wording of guideline recommendations, the choice of appropriate practice points (with guidance from the Methods Committee representative), and supporting materials. WG members are authors of the guideline and must adhere to the ICMJE authorship standards, but they should also follow the rules of guideline writing developed by KDIGO. However, WG members are usually chosen for their expertise in understanding and interpreting the subject matter encompassed by the guideline and not because of their experience or expertise in writing guidelines. Therefore, the WG must rely on the ERT and KDIGO team for guidance in writing the guideline. Cooperation between everyone involved in producing a guideline is key to successfully and transparently communicating evidence-based guideline recommendations and their development and rationale.

WG responsibilities

When it comes to writing the guideline, the WG has three main responsibilities:

- Draft guideline recommendations and practice points
- Format recommendations and practice points, including supporting text
- Develop figures and tables for guideline publication

Drafting and format of guideline statements

Recommendations

Recommendations should be formatted as actionable statements: [What] should be done in [whom], [when], and [how].

Example: We suggest that class II lupus nephritis with albuminuria >3 g/d be treated at diagnosis with corticosteroids or CNIs as described in Table X.

A recommendation can be either positive (i.e., do X) or negative (i.e., do not do X). It is important to make the wording as clear and unambiguous as possible:

- Make recommendations actionable. <u>If it does not imply an action, it is not a recommendation</u>.
- Negative statements are acceptable if you “recommend/suggest” *not* doing something. Be sure that *not* follows recommend/suggest as opposed to *not* recommending/suggesting something.
    - “We recommend *not* using …” **(Correct)** vs. “We *do not* recommend using …” **(Incorrect)**
- Avoid infinitives (e.g., “to error is human”)
- Do not use “may,” “can,” and “might” in the recommendation.
- Avoid “should” and “consider.”

Grading the strength of the recommendations

Recommendations are followed by declarations of the strength of the recommendation and the certainty of the evidence which underlies that recommendation. The two options for strength of recommendation are strong and weak/conditional (Table 13).

Table 13. Implications of strong vs. weak/conditional recommendations

	Patients	Clinicians	Policy
1. Level 1, strong "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
2. Level 2, weak/conditional "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

The WG is primarily responsible for grading the strength of a recommendation. The strength of a recommendation is determined by the evidence on the balance of benefits (desirable effects) and harms (undesirable effects), certainty of the evidence, patients' values and preferences (e.g., how much the desirable and undesirable effects are valued, and how values differ between patients), and resource use and costs needed. There are other often complex judgments regarding the size of the net medical benefit, variability in patients' values and preferences, and costs, particularly for international guidelines. These aspects should be considered when grading the strength of recommendations, and the WG's discussion about them should be reported in the rationale supporting the recommendation (Table 14).

Table 14. Factors that influence the strength of a recommendation

Factor	Comment
Balance of benefits and harms	The larger the difference between desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak/conditionalrecommendation is warranted.
Quality of evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preference, the more likely a weak/conditional recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention – that is, the more resources consumed – the less likely a strong recommendation is warranted.

Besides grading the strength, each recommendation is followed by information on the certainty of its underlying evidence. As discussed, the certainty of evidence is primarily graded by the ERT, although the WG has input.

An example of a recommendation and the accompanying grading of strength of recommendation and certainty of evidence:

> We suggest that class II LN with proteinuria >3 g/d be treated at diagnosis with corticosteroids alone or in combination with a CNI as described in Table X. (2C)

Writing the supporting text for recommendations

Remark

Follow the recommendation with a short remark (1-2 sentences), which quickly summarizes the most important factor(s) that you considered when making this recommendation.

Since one key difference between strong and weak/conditional recommendations is the proportion of patients who should follow the recommendation, WG members should guide practitioners by expanding the remark to explain who might not follow the recommendation, that is, what clinical circumstances/patient preferences/other factors would influence this decision. If it is difficult to think of circumstances where the recommendation might not be followed, then maybe it should be a strong recommendation. Therefore, weak/conditional recommendations should always be followed by a sentence or sentences that explain for which groups of patients the recommendation may be less appropriate.

> Example: We suggest that class II LN with proteinuria >3 g/d be treated at diagnosis with corticosteroids alone or in combination with a CNI as described in Table X. (2C)
>
> *This recommendation places a relatively higher value on preventing the complications of nephrotic syndrome, progressive kidney failure from LN, or relapse of proteinuria, and a relatively lower value on adverse events related to adverse effects of corticosteroids or CNIs. Patients who are more concerned about or at higher risk for medication-related adverse effects may choose not to receive some or all of the suggested treatments.*

Key information

This section immediately follows a recommendation or groups of closely related recommendations. It should address all four elements in Table 14 (Balance of benefits and harms; Certainty of evidence; Values and preferences; Resource use and costs). These elements should be discussed in sequence to provide a “chain of logic” that explains the basis for the recommendation. They should be followed by a fifth element (“Considerations for implementation”) that may inform uptake of the recommendation. Some additional detail is provided below.

Balance of benefits and harms

For recommendations about testing and evaluation, the text should explain how the recommendation will help to identify individuals at increased risk (or those suitable for treatment) and how following the recommendation will translate into better outcomes. Potential negative consequences of such testing that should be weighed against these benefits include over-diagnosis, false positives, labeling, harms, and costs of follow-up testing/treatments, etc.

For recommendations about treatments, the text should discuss the effectiveness and safety of certain interventions compared to other treatment alternatives.

This section should summarize what the evidence says about the net benefit across all important outcomes and should refer back to the EvP/SoF tables from the ERT as much as possible. The ERT will be responsible for reviewing and confirming the relevant text is accurate. Risk estimates from the evidence review should be cited where applicable, but a full summary of all data from the summary tables does not need to be repeated in the text.

Example: This recommendation relies heavily on the original NIH trial of cytotoxic agents added to corticosteroids that demonstrated long-term benefit for kidney survival compared to corticosteroids alone. Given the toxicity of high-dose cyclophosphamide, RCTs have demonstrated equivalent long-term effectiveness of low-dose cyclophosphamide in some LN populations, including Caucasian and Indian patients, but with fewer adverse effects. Short-term induction of response trials has shown that MMF is equivalent to cyclophosphamide, but long-term kidney survival data comparing the two regimens is not available. Short-term induction-of-response trials have shown that the addition of a CNI to reduced-dose MMF and corticosteroids is superior to cyclophosphamide for induction of renal response, but extended follow-up shows equivalence. Key missing data are trials demonstrating that short-term renal response equates to long-term kidney health. Also, the optimal duration of CNI treatment is not defined, and disease flare after stopping CNI is a concern.

Certainty of evidence

The ERT should summarize how the evidence supports the recommendation. This can follow the summaries in the evidence profiles, if available.

The ERT should also discuss limitations in the evidence base and how this affected the grading for certainty of evidence. Distinguish absence of evidence (i.e., studies have not been done or have been done and are inconclusive) from evidence of absence (i.e., studies show that a particular treatment is ineffective).

The WG should review and approve these sections, but the ERT should provide the initial draft of the text.

Values and preferences

Describe how the WG applied its assessment of values and preferences to the evidence when drafting the recommendation. Which factors were considered most important, and which were

considered less important? This section can expand on the text that immediately follows the recommendation.

In the example above, *"This recommendation places a relatively higher value on preventing the complications of nephrotic syndrome, progressive kidney failure from LN, or relapse of proteinuria, and a relatively lower value on adverse events related to adverse effects of corticosteroids or CNIs."*, this section might summarize why the WG thinks that most patients would prioritize avoiding kidney failure over side effects due to immunosuppressive treatment.

"The recommendation is strong because the Work Group judged that all or nearly all well-informed patients would choose to receive eight weeks of corticosteroids as initial treatment of MCD, compared to a longer course of corticosteroids, another treatment or to no treatment."

Resource use and costs

Explain how the WG incorporated information on resource use into the recommendation. Examples of resource use include health care costs as well as out-of-pocket costs for patients and families.

Since KDIGO guidelines are used worldwide, it is important to consider how resource use may vary across countries. In some cases, it may make more sense to consider relative costs (e.g., treatment A costs several times as much as treatment B) as opposed to absolute costs (e.g., treatment A costs $500 whereas B costs $95).

When a treatment is very costly but also very effective, it may also be appropriate to make a weak/conditional recommendation for treatment rather than recommending against treatment solely on the basis of resource use. In such cases, the explanatory text following the recommendation can be used to explain that the treatment will be most suitable for those who can better afford it.

Example: We recommend that XYZ be used to treat class IV LN in people with good functional status and eGFR 15-30 ml/min/1.73 m² at diagnosis. (2A)

This recommendation places a relatively higher value on strong evidence that XYZ safely prevents kidney failure in this patient population, and relatively lower value on the high cost of XYZ. Patients with limited financial resources or treated in health systems where XYZ is less available or affordable may be less inclined to follow this recommendation."

Considerations for implementation

The section on Considerations for implementation should address consideration in conceptualizing the recommendation to better facilitate the adaptation of the recommendation in local or regional settings.

In addition, differences in various populations should be addressed in this section. For example, are there any differences between (a) men and women, (b) people of different ethnic backgrounds/races, or (c) people from different health systems that could be considered for implementation?

For example, DDAVP doses should be ~50% lower in women than men due to genetic differences in the vasopressin receptor. And in Asia, there is a widespread belief/some data that doses of statins should be lower for Asian people than those routinely used in the West. Are there similar considerations for your recommendation?

Rationale

This brief section has two purposes. First, to expand on the short remark that immediately follows the recommendation summarizing how the WG considered the four factors in the Key Information section when drafting the recommendation.

Second, (if applicable) to explain any key differences between the current KDIGO recommendation and recommendations made by other guideline producers. Examples of factors that might explain differences in recommendations include different populations (e.g., CKD vs. general population), new evidence, different values and preferences, etc.

Practice points

Overview

Historically, KDIGO guidance has included many ungraded statements. KDIGO has decided that ungraded statements will no longer be used (except in very rare instances). A limited number of practice points may be included in KDIGO guidelines. Unlike recommendations, practice points are not graded for strength of recommendation or certainty of evidence, and practice points are not based on the findings of evidence reviews. The most frequent circumstance under which practice points are used concerns the implementation of recommendations, such as the frequency of laboratory monitoring and clinic visits, criteria for referral to specialist care, etc.

Practice points can be formatted as text, but text is often not the best format. Guiding the clinician in the form of practice points may be easier if they are formatted as a table (e.g., info on treatment, dose/duration, regimens), a figure, a box, or an algorithm. Supporting text and references can be provided where appropriate.

Because practice points add length to the guideline document (and consume the WG's time), the WG should carefully consider which practice points should be included. Only points that are truly necessary should be included. Note that practice points do not need to appear at the end of the text but may be interspersed with recommendations to improve the flow of the document.

Criteria for using practice points

First, practice points may only be used if no evidence review was done to address the relevant key question. If a systematic review addresses the relevant question, the guideline must either remain silent on that issue or provide guidance in the form of a structured recommendation.

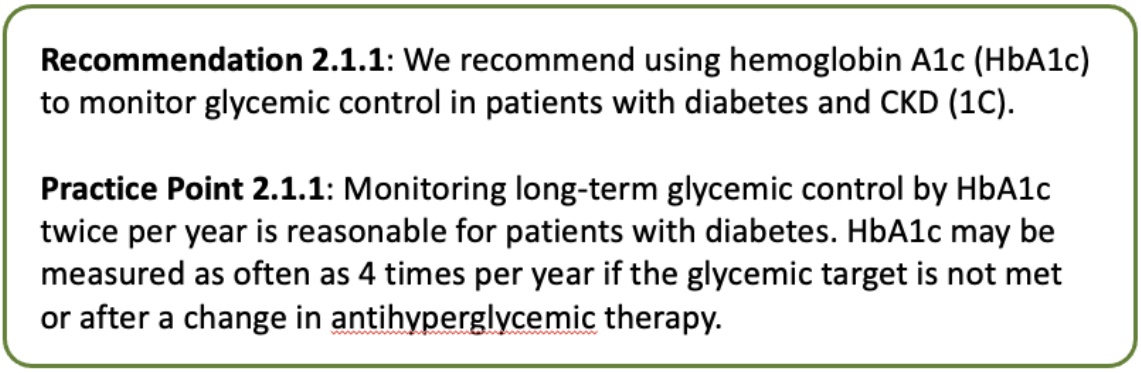
Second, practice points may not be used to provide guidance on issues that require consideration of patients' values and preferences. For example, a practice point that advised the use of genetic testing would not be appropriate, since such testing does require a discussion of values and preferences with patients and families.

Third, practice points may not be used to advise actions that have substantial resource implications. For example, a practice point that advised clinicians to arrange magnetic resonance imaging for all patients who met certain criteria likely would not be appropriate, since the substantial resource use that would follow should be justified by a full discussion of the clinical benefits.

Types of practice point

Provided the three criteria above are met, there are five broad circumstances under which practice points may be used. The first is where the WG wants to provide guidance on how to implement a particular recommendation, and the practice point is linked to that recommendation. For example, a recommendation might advise the use of HbA1C to monitor glycemic control in patients with diabetes and CKD, whereas a linked practice point might suggest that HbA1C could be measured between two and four times per year, depending on certain factors (Figure 5).

Figure 5. Example of linked recommendations and practice point



The second concerns situations where the WG wants to provide guidance on how to implement a group of recommendations, such as three to four recommendations on the choice of glucose-lowering drugs in people with diabetes and CKD. In this circumstance, the focus of the practice point remains on implementation, but there is no specific recommendation to which the recommendation is linked (Figure 6).

Figure 6. Example of implementation practice point

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 20).

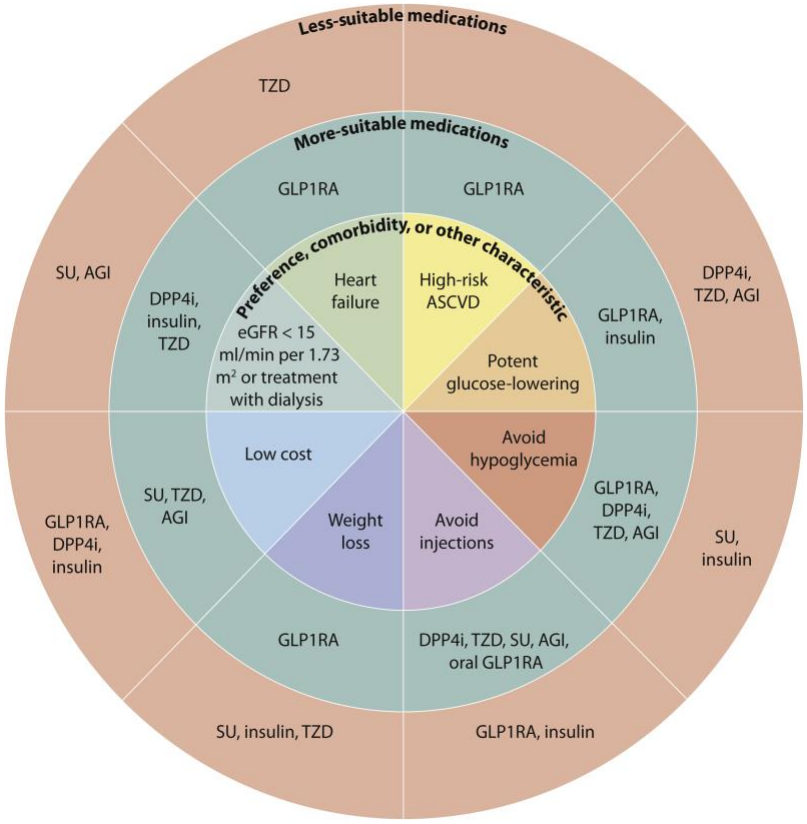


Figure 20 | Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD. AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

The third circumstance is where the WG wants to give advice on clinical management. The question is not testable because the comparator is implausible or absurd, so no systematic review was done. Nevertheless, the WG feels it is important to provide this guidance to clinicians. An example of such a practice point would be, “In patients with AKI, it is important to exclude obstruction using a kidney ultrasound or other appropriate imaging test.”

The fourth circumstance is where the WG wants to give advice on clinical management about a question that is testable but for which no systematic review was done (for example, because the question was not anticipated during Meeting Zero, because the systematic review would be very onerous, or because resource limitations precluded the review from being done). This type of practice point effectively becomes a strong recommendation without any supporting evidence or discussion of benefits, harms, preferences, or costs. Therefore, these practice points should be used very infrequently, if at all. An example of a practice point in this category appears in Figure 7.

Figure 7. Example of practice point developed for a testable question without a systematic review

Practice Point 3.1.2: Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent (Figure 29).

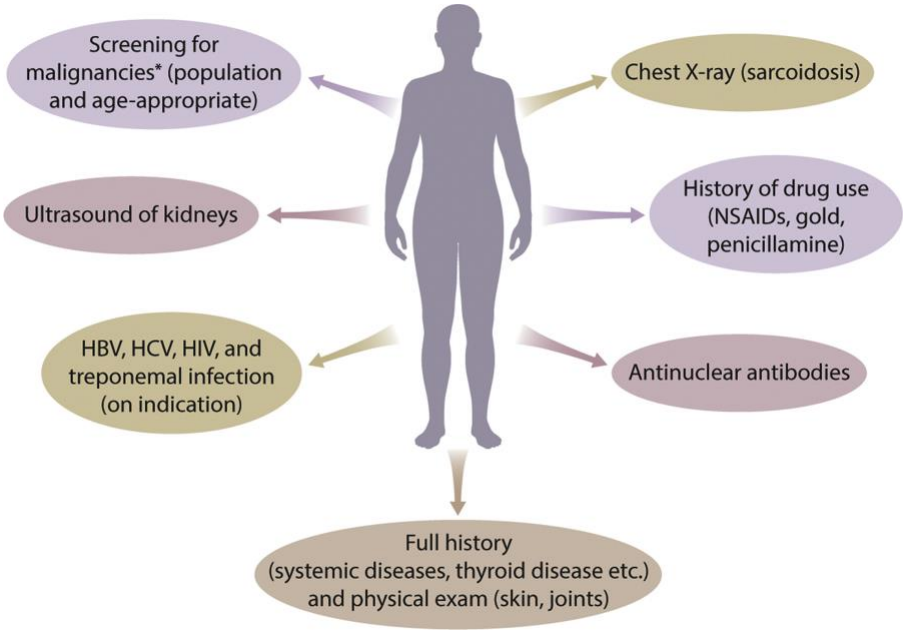


Figure 29 | Evaluation of patients with MN for associated conditions. Patient with MN should be evaluated for associated conditions, independent of the presence or absence of anti-PLA2R antibodies or anti-THSD7A antibodies. *Varies per country; the yield of cancer screening is not very high, especially in younger patients. Many centers will perform chest X-ray or computed tomography (CT) scan, look for iron deficiency, and require the patients to participate in the national screening program for breast and colon cancer; a prostate-specific antigen (PSA) test is done in adult males aged >50–60 years. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

The fifth and last circumstance concerns advice on nomenclature. For example, the WG may choose to advise clinicians to classify CKD using a recommendation, e.g., “We recommend that clinicians diagnose CKD in patients who have abnormalities of kidney structure or function that are present for more than three months and have implications for health.” Alternatively, the WG could use a practice point to give the same advice, perhaps using a table, figure, or algorithm to present the guidance.

Research recommendations

These can be bullet points focusing on those issues that would be most useful to inform future recommendations on this topic. Avoid making a large number of research recommendations that are not feasible at this time.

Development of graphics for guideline publication

The use of infographics in KDIGO guidelines is highly encouraged. Often, a figure or table will be able to present the necessary information in a more succinct way than trying to explain the same concepts in text (see above for examples).

KDIGO works with a medical graphic designer who is able to turn hand sketches, existing figures, or Office (i.e., Word, PPT, etc.) versions of the graphic into final versions to be used in the final publication of the guideline.

ERT responsibilities during the writing process

The ERT reviews all guideline recommendations from the WG and suggests corrections or clarifications in wording. The WG and the ERT work together to reach a consensus on the wording, the strength of a guideline recommendation, and the certainty of evidence for a guideline recommendation. In general, the ERT should have the final say in assigning the certainty of evidence (i.e., A, B, C, D), given the experience and training of the ERT. The WG should have the final say on the strength of the recommendations (i.e., Level 1 and Level 2) and wording of recommendations and practice points.

Confirm all statements in the supporting text that refer to the evidence reviewed

Each guideline recommendation is followed by a section on Key Information. The WG drafts the subsections on the Balance of benefits and harms, which the ERT then reviews to ensure that interpretations of the data are accurate. Similarly, the ERT drafts the Certainty of evidence section, which should be reviewed and approved by the WG. The WG drafts the remaining subsections of Key Information, which the ERT will review and suggest changes as needed.

Each guideline recommendation also includes a section on Rationale. The Rationale section is drafted by the WG and is designed to allow the WG to explain how the evidence links to the guideline recommendation and the WG's reasoning for the recommendation. The ERT reviews each Rationale section of the guideline.

Reference supporting summary tables and evidence profiles/summary of findings tables

The ERT is responsible for inserting all EvP/SoF table callouts in the appropriate places in the guideline supporting text and ensuring that all evidence profiles are referenced correctly.

Development of a Methods Chapter and Data Supplement

The ERT is responsible for the development of the Methods Chapter and Data Supplement that accompany the guideline publication.

The Methods Chapter describes how the ERT interacts with the guideline WG to produce the systematic review, the summary tables, the guideline recommendations, the strength of guideline recommendations, the strength of evidence according to GRADE, as well as how the ERT participates in the writing of the guideline’s supporting text.

The Data Supplement includes the search strategies that were used in the evidence reviews. It will also include the EvP/SoF tables.

Public review of the draft guideline

As with the Scope of Work, the public has an opportunity to make comments and suggestions on the guideline in its near-final form during a public review phase. This is the second opportunity for external stakeholders to play a role in the development of KDIGO guidelines. Comments are sought from researchers and clinicians, industry, patients and caregivers, other organizations, and health policy makers. A full month is usually allowed for this comment period, but it may be extended if necessary. A similar process as for the Scope of Work is followed to elicit feedback for public review (see above).

Response to feedback from public review

The steps taken to address the public review feedback include:

1. Comments are circulated to the full WG.
2. The KDIGO team summarizes comments into a document of key concepts.
3. Co-Chairs review the key concepts document to adjudicate what is or is not necessary to address.
4. The key concepts document is shared with the small writing groups.
5. Chapter calls are held as needed. This is usually reserved for topic areas where some controversy (i.e., low approval ratings) was identified in feedback from the public review.
6. The WG revises their sections (timeline is approximately two to three weeks).

The WG must consider the comments made during public review, but the final guideline content is the responsibility of the WG.

Update of evidence reviews

During the public review process, the ERT is tasked with updating the evidence reviews for new evidence published since the initial search.

Search updates within the timeline of the guideline should, in general, be identical to the literature searches done at initiation of the evidence review. If the WG determines that any specific topic does not require a search update, this caveat needs to be made explicitly in all descriptions of the search and the protocols of the evidence review. Depending on the literature database being re-searched, it is standard practice to include a 6-12-month overlap between the initial search and the updated search.

The update process should follow all steps for the initial review, and all deliverables should be updated accordingly.

Finalizing the guideline

Confirm all data prior to guideline publication

Before the guideline is submitted to a journal, it is the responsibility of the ERT to review and confirm evidence review data cited correctly. This includes a final data check for all data numbers (number of studies/patients, effect estimates and CI, p-values, etc.). In addition, the ERT should also confirm all callouts to the EvP/SoF tables presented in the Data Supplement.

Voting/reaching consensus

KDIGO does not require there to be a vote on every recommendation or practice point; however, when there is not consensus among the Work Group, the Guideline Co-Chairs have the option to call for a formal vote on a specific statement. The results of this vote should be made transparent within the guideline itself, and the dissenting parties should be tasked with writing a short description of their opinion to be included in the guideline.

The use of informal votes (e.g., straw polls) may be useful when gauging consensus on recommendations or practice points but is also not required.

When there is no consensus between the ERT and WG, the WG will have the final say on whether to develop a recommendation or practice point and the strength of the recommendations (i.e., Level 1 and Level 2). The ERT should have the final say in assigning the certainty of evidence (i.e., A, B, C, D), given the experience and training of the ERT. The wording of both recommendations and practice points will be based on consensus among all parties (WG, ERT, Methods Committee representative).

Review of the guideline development process

Several tools and checklists have been developed to assess the quality of the methodological process for evidence review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE II) criteria, the Conference on Guideline Standardization (COGS) checklist,[28] and the National Academy of Medicine (formerly Institute of Medicine) Standards for Systematic Reviews and Clinical Practice Guidelines We Can Trust.[23]

Appendix C. Checklists to assess the quality of the methodological process for systematic review and guideline development shows the AGREE II and COGS checklist.

Journal submission

KDIGO guidelines should be disseminated as widely as possible to those who will use them. KDIGO holds the copyright to all KDIGO guidelines and makes guidance available free of charge on the KDIGO website. However, KDIGO also publishes guideline products (including translations and summaries) in the most appropriate medical journals.

KDIGO Guidelines have traditionally been published in *Kidney International (KI)*, the official journal of the International Society of Nephrology (ISN). The ISN is the only major professional society representing the entire global nephrology community. Similarly, transplant-related guidelines have been published in *Transplantation*, the official journal of The Transplantation Society (TTS). The TTS is the only major professional society representing solid organ transplantation in all countries around the world. Since KDIGO Guidelines are global, publication in global journals meets the needs of KDIGO and the professional societies representing the KDIGO targets audience.

The KDIGO team works on preparing the document for publication. This includes reference management, adherence to the style and requirements of the journal, collection of permissions for the reuse of figures, review and editing of page proofs, and signing off on the final manuscript. The team secures author statements on financial interests and copyright clearances. They also negotiate page charges with the publisher.

KDIGO usually allows figures and tables from the KDIGO guidelines to be reproduced by authors of other articles. However, KDIGO does not assume rights or responsibilities of these independent articles.

For all KDIGO publications, KDIGO adheres to the recommendations of the International Committee of Medical Journal Editors (ICMJE) regarding authorship.[29] This usually means that all WG members are authors of the guideline that they help to produce.

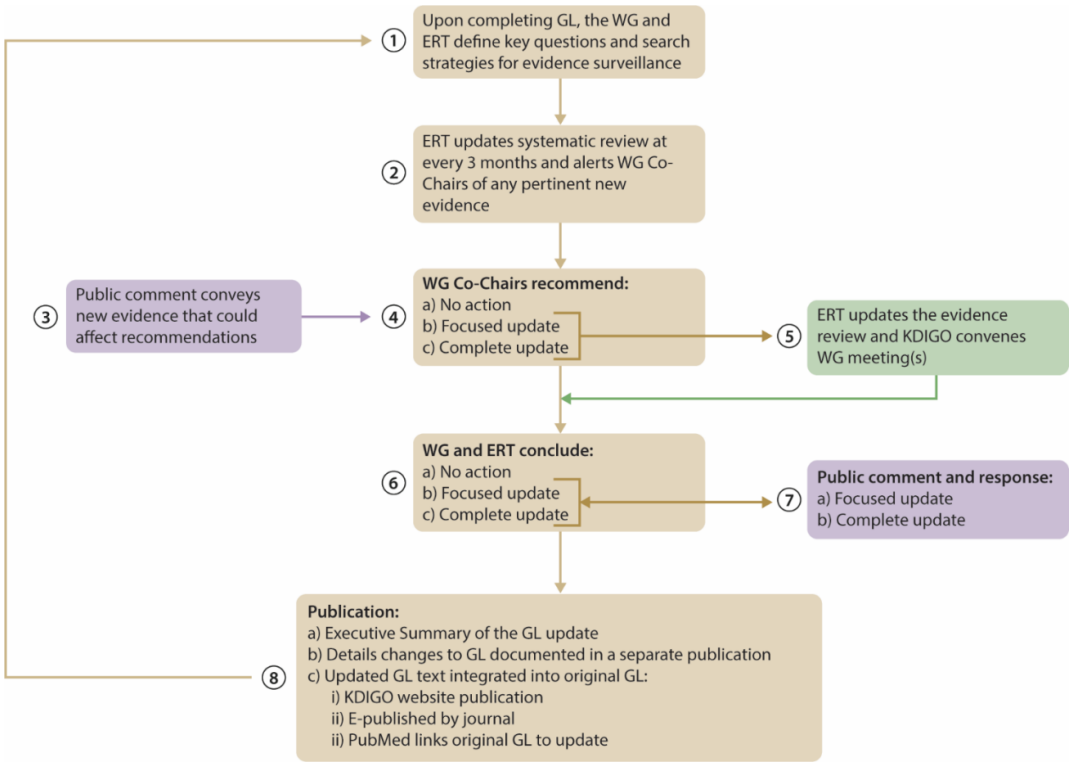
Guideline update process

Like other organizations producing evidence-based clinical practice guidelines, the major challenge for KDIGO is updating guidelines in a timely and efficient manner. As time passes, more and more of the time and effort from KDIGO need to be on updating guidelines rather than on developing new guidelines.

For KDIGO, key elements in this process include (Figure 8):

- Beginning the process as soon as a guideline or guideline update is completed
- Maintaining continuous updating of evidence by a qualified ERT
- Communicating to the WG Co-Chairs when new evidence becomes available that could require a major or minor modification of a guideline recommendation
- Reconvening the guideline WG and ERT to review the new evidence and modify the pertinent guideline recommendations
- Publishing the updates in a timely manner
- The process then begins again

Figure 8. Keeping KDIGO guidelines up to date



ERT, Evidence Review Team; GL, guideline; KDIGO, Kidney Disease: Improving Global Outcomes; WG, Work Group

Evidence surveillance

Upon completing a guideline, the WG and ERT define key questions and search strategies for future surveillance and updates (Figure 8).

Evidence surveillance is a 3-phase process as outlined below:

- **Phase 1: Basic Surveillance**
  - Run quarterly literature searches in various medical databases for new studies or publications using existing search strategies
  - Screen eligible studies - RCTs and observational data (as needed)
- **Phase 2: Produce an Evidence Summary**
  - Evidence maps with basic PICOS data extraction
  - Provide a summary of eligible studies to KDIGO leadership for an update decision
- **Phase 3: Evidence Synthesis**
  - Usually done when a decision to update has been made
  - Data extraction
  - Critical appraisal
  - Meta-analysis
  - Evidence tables

Evidence review updates

When possible, the same ERT that performed the evidence reviews and worked with the WG to produce the original guideline should be contracted to continually update the systematic reviews. When the ERT becomes aware of a new study or piece of information that could potentially alter a guideline statement, they should immediately notify the WG Co-Chairs. The new information could be the publication or presentation at a meeting of results from a well-designed, randomized controlled trial. However, the new information could also be notification of removal from the market of a therapeutic agent that is critical to carry out a specific guideline recommendation. The WG Co-Chairs use this information to decide what next steps should be taken.

Determination of appropriate action

When new evidence pertinent to one or more guideline recommendations becomes available, the WG Co-Chairs are charged with recommending what additional steps should be taken. Of course, the WG Co-Chairs may consult with the rest of the WG and with the KDIGO Co-Chairs in making these decisions.

The WG Co-Chairs may decide that no further action is required other than to continue watching for additional evidence. They may also decide that a single guideline recommendation may need to be altered. In this case, it may be sufficient to convene the guideline WG for a single teleconference that reviews the evidence and ultimately suggests a specific revision be made to a guideline recommendation or practice point.

This proposed revision could be posted for public comment and then submitted for publication, all in a very short timeframe. Alternatively, the WG Co-Chairs could recommend to KDIGO a more extensive revision or even a complete reworking of the guideline following the usual KDIGO process and procedures.

Convening the Work Group

The WG Co-Chairs maintain close contact with the KDIGO team. Actions such as reconvening a guideline WG require adequate resources, and guideline development must be prioritized by the KDIGO Co-Chairs and Executive Committee. Whatever actions are taken are orchestrated by the KDIGO team on behalf of the guideline Co-Chairs and the guideline WG.

Guideline updates

Minor changes to one or two guideline statements may be made quickly and efficiently. However, more extensive changes may require a much greater commitment from the WG Co-Chairs and WG. In fact, it may end up being a good time to replace all or some of the members of the guideline WG with new volunteers who are willing to carry the effort forward.

Publication

When a guideline WG decides to change a single statement, the process may occur very quickly (e.g., within a month or two). The updated information could be made by the journal publishing the original guideline through the same mechanisms as an erratum or letter to the editor linking/cross-marking to the original manuscript. This would then link the change/update to the original published guideline through online citation services. Therefore, a search for the original guideline will produce a notification of the linked update. Of course, all of these considerations depend on arrangements made with the journal.

Alternatively, a major revision of a guideline will result in it being published anew through the usual mechanisms. Anytime there is a guideline update, the complete revised guideline, even with only minor modifications, can be made available on the KDIGO website.

Implementation and dissemination

Dissemination

It is the goal of KDIGO to provide a core suite of implementation tools for every guideline it produces. To this end, a brief guideline Executive Summary, which distills the key guideline messages, is published in *Kidney International* in tandem with the full-length guideline that appears in *Supplement to Kidney International*. For broader outreach, KDIGO also aims to produce a guideline synopsis in *Annals of Internal Medicine* for guideline topics that are of potential interest to the larger medical community. KDIGO has also endeavored to publish case-based studies to illustrate how its recommendation statements and practice points can be applied in real-world settings. Other ancillary publications may be undertaken as journal interest and Work Group resources allow.

Authorship

It is a longstanding KDIGO policy to reserve authorship of our full-length guidelines solely to the Work Group members. This is a way for KDIGO to acknowledge the WG members' years-long volunteer service from the initial planning, formulation/writing, and implementation phases for a given guideline.

KDIGO also values the assistance provided by the ERT and Methods Committee members. To acknowledge their contributions to a guideline, KDIGO regularly includes the (co)directors and project leads from the ERT as well as the Methods Committee representative in as many ancillary publications as possible, including but not limited to the Executive Summary manuscripts in *Kidney International* and guideline synopses in *Annals of Internal Medicine*. In addition, KDIGO encourages the ERT to develop dedicated publications based on guideline evidence reviews.

Implementation

In addition to the ancillary publications above, KDIGO also develops resources to enhance the uptake and dissemination of guideline content by clinicians. These resources include a Speaker's Guide, which contains accompanying guideline notes and all of published figures to facilitate distribution and knowledge translation. Summaries of salient guideline messages in the form of "Top 10 Key Takeaways" are also furnished as part of this implementation portfolio. Where applicable, a guideline Central Illustration is also developed. Other implementation tools, such as guideline infographics or point-counterpoint tools, may also be developed.

KDIGO also partners with local or regional nephrology societies in presenting its guidelines at national meetings or congresses. Depending on availability of resources and opportunities, KDIGO strives to produce an additional array of dissemination tools to further aid clinical decision-making. These include but are not limited to:

- Reference guides (e.g., clinician foldout tools, pocket cards, handouts)
- Visual guidelines (i.e., guidelines that are rendered in algorithm or flow-chart format)
- Guideline translations
- Video summaries of key guideline takeaways
- Live presentations/Implementation Summits, webinars/expert videos, podcasts, tweetorials, guideline infographics/Visual Abstracts, etc., in partnership with regional nephrology societies or nephrology education platforms such as NephJC, GlomCon, Arkana, etc.

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Appendix A. Examples of competing interests and management

[High-risk] Example 1: Personal financial, Specific:

Consultancy fee received by a Work Group member from the company producing a product in the class of therapies under consideration, or a product in the comparator class

Action required: Depends on the nature of the consultancy undertaken and the details of the guideline.

- Exclusion from Work Group – if the interest relates specifically to a product under consideration, or its comparator and is judged of sufficient relevance, magnitude, and/or recency to preclude objectivity or the appearance of objectivity. The interest is a specific, personal, financial interest.
- Withdraw from discussion and decision-making on the specific matter -- if the interest relates specifically to a product under consideration, or its comparator, but its relevance, magnitude, and/or recency are not judged to preclude objectivity or the appearance of objectivity. The interest is a specific, personal, financial interest.
- Declare and remain – if the consultancy is unrelated to a specific product under consideration for the guideline or its comparator. The interest is not specific.

[Moderate risk] Example 2: Personal non-financial, Specific

A member of the Work Group for the guideline on condition A has published several papers supporting the use of drug X as first line management of condition A, including a randomized trial and two review articles. The WG is now discussing treatment options for condition A.

Action required: Withdraw from discussion and decision-making on the specific matter – this is non-financial, personal, and professional interest, and the response will depend on the nature of the view expressed and the risk to perceived objectivity. In determining the level of involvement, the Guideline Chair(s) should consider the balance between this risk and the benefit of the member's input to the Guideline Work Group. In this example, the WG member might derive considerable professional benefit if drug A were recommended as the first-choice treatment in KDIGO guidance on condition A. Therefore, this interest may compromise the member's objectivity (or perceived objectivity), and exclusion may be most appropriate. Open declaration or partial exclusion (i.e., the member remains in the room to answer questions but does not take part in decision-making) will often be sufficient.

In contrast, a WG member who wrote a review article on condition X might not necessarily have a relevant non-financial interest, unless the article took an unusually strong position on drug A or an alternative.

[Low risk] Example 3: Non-personal financial, Specific

Grant income received by the Work Group member's employer from the company that manufactures the product.

Action required: Declare and remain – this is a non-personal, financial interest. Because the income goes to the employer, there is no strong conceptual link between this publication and potential benefit to the WG member, regardless of what the guideline recommends. Therefore, there is no realistic threat to objectivity.

[Low risk] Example 4: Personal financial, Non-specific:
Consultancy fees received by a Work Group member from a company with a product unrelated to the guideline

Action required: Declare and remain – there is no strong conceptual link between this publication and potential benefit to the WG member, regardless of what the guideline recommends. Therefore, there is no realistic threat to objectivity.

[Low risk] Example 5: Personal non-financial, Non-specific
Research publications covering epidemiology of condition X, for a WG member on a guideline panel for condition X, where condition X is a complication of CKD.

Action required: None –there is no strong conceptual link between this publication and potential benefit to the WG member, regardless of what the guideline recommends. Therefore, there is no realistic threat to objectivity and action is not required.

[Low risk] Example 6: Non-personal financial, Non-specific
The member's institution or organization receives government funding for evidence reviews not related to the guideline topic.

Action required: These interests typically do not require disclosure except under exceptional circumstances. Again, the test is whether the interest could be perceived as compromising the integrity of the guideline. For example, if a government had a strongly stated policy position that was relevant to a guideline, and if contravening that position could conceivably lead to the withdrawal of funding from the member's institution, then in theory, this interest might require disclosure and management. In practice, such circumstances are unlikely to occur.

Appendix B. Disclosures of interest form

KDIGO Form* for Disclosure of Potential Competing Interests

1. INSTRUCTIONS

This form will provide the public with information about your other interests thatcould influence how they perceive your work for KDIGO. All KDIGO volunteers should submit a form and vouch for its accuracy. This is part of the KDIGO commitment to total transparency in all its activities.

2. IDENTIFYING INFORMATION

1. Given Name (First Name): Click or tap here to enter text.
2. Surname (Last Name): Click or tap here to enter text.
3. Date: Click or tap here to enter text.
4. Title and Organization/Affiliation: Click or tap here to enter text.

3. RELEVANT ACTIVITIES

This section asks about your financial relationships with industry, non-government, and government bodies and non-financial interests that may give the appearance of potentially influencing your work with KDIGO. You should disclose interactions with any entity that might be considered broadly related to the work being conducted for KDIGO or for the topic under consideration (e.g., the topic of the guideline for which you will be a Work Group member).

Report all sources of revenue paid (or promised to be paid) directly to you or to your institution on your behalf over the last 24 months.

Regarding non-financial interests, it is expected that you will have previous activities that are

*Adapted from ICMJE

conceptually linked to your work with KDIGO.

Place an “x” in the appropriate boxes to indicate whether you have financial relationships with entities (>€500) or non-financial interests as described in the instructions. You should report relationships that were present during the last 24 months or that you expect within the next 12 months. Complete each question by selecting “None” or providing the requested information. For examples of the various types of interest, please see **Appendix A. Examples of competing interests and management**. All questions refer to your work with KDIGO or the topic under consideration related to your work with KDIGO.

Financial disclosures of interest

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Comments
1	Support for any study or manuscript pertaining to the topic of interest (e.g., funding, provision of study materials, medical writing, article processing charges)	☐ None Entity | Paid to you | Paid to institution | Relevant to topic of interest | Not relevant to topic of interest ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
2	Grants or contracts from any entity (if not indicated in item #1 above) related to the topic of interest	☐ None Entity | Paid to you | Paid to institution | Relevant to topic of interest | Not relevant to topic of interest ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
3	Royalties or licenses	☐ None Entity | Paid to you | Paid to institution | Relevant to topic of interest | Not relevant to topic of interest ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
4	Consulting fees	☐ None Entity | Paid to you | Paid to institution | Relevant to topic of interest | Not relevant to topic of interest	

			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
5	Payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events	☐ None					
		Entity	Paid to you	Paid to institution	Relevant to topic of interest	Not relevant to topic of interest	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
6	Payment for expert testimony	☐ None					
		Entity	Paid to you	Paid to institution	Relevant to topic of interest	Not relevant to topic of interest	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
7	Funding for travel and/or accommodation	☐ None					
		Entity	Paid to you	Paid to institution	Relevant to topic of interest	Not relevant to topic of interest	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
8	Patents planned, issued, or pending	☐ None					
		Entity	Paid to you	Paid to institution	Relevant to topic of interest	Not relevant to topic of interest	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☐ None					
		Entity	Paid to you	Paid to institution	Relevant to topic of interest	Not relevant to topic of interest	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
			☐	☐	☐	☐	
10	Any ***paid*** leadership or	☐ None					

	fiduciary role in other board, society, committee, or advocacy group relevant to the topic of interest	Entity / Paid to you / Paid to institution ☐ ☐ ☐ ☐ ☐ ☐
11	Stock or stock options	☐ None Entity / Paid to you / Paid to institution / Relevant to topic of interest / Not relevant to topic of interest ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
12	Receipt of equipment, materials, drugs, medical writing, gifts, or other services	☐ None Entity / Paid to you / Paid to institution / Relevant to topic of interest / Not relevant to topic of interest ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
13	Other ***financial*** interests relevant to the topic of interest	☐ None Entity / Paid to you / Paid to institution ☐ ☐ ☐ ☐ ☐ ☐

Non-financial disclosures of interest

		Other relationships, activities, or publications that a reasonable person might perceive as potentially influencing your work with KDIGO. Unsupported research publications on a given drug or condition, membership of governmental, non-governmental, advocacy, or lobbying organization, and serving as an expert witness are all examples of non-financial interests that should be disclosed; other examples exist. Please see Appendix A for more details.
1	Any ***unpaid*** leadership or fiduciary role in other board, society, committee, or advocacy group relevant to the topic of interest	☐ None Entity / Paid to you / Paid to institution ☐ ☐ ☐ ☐ ☐ ☐

2	Other ***non-financial*** interests relevant to the topic of interest	☐ None ☐ Yes If yes, please describe	

Appendix C. Checklists to assess the quality of the methodological process for systematic review and guideline development

Appendix Table C1. AGREE Reporting Checklist (2016)

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE and PURPOSE		
1. OBJECTIVES Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.	☐Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS Report the health question(s) covered by the guideline, particularly for the key recommendations	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply	☐ Target population, sex, and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence, and individuals involved in formulating the final recommendations.	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	
5. TARGET POPULATION PREFERENCES AND VIEWS Report how the views and preferences of the target population were	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)	

sought/considered and what the resulting outcomes were.	☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS Report the target (or intended) users of the guideline.	☐ The intended guideline audience (e.g., specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS Report details of the strategy used to search for evidence	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004, to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	
8. EVIDENCE SELECTION CRITERIA Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale where appropriate.	☐ Target population (patient, public, etc.) ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☐ Appropriateness/relevance of primary and secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies	

that can facilitate the reporting of this concept	☐ Magnitude of benefit versus magnitude of harm ☐ Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations, and the final vote)	
11. COMDINERATIONS OF BENEFITS AND HARMS Report the health benefits, side effects, and risks that were considered when formulating the recommendations.	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE Describe the explicit link between the recommendations and the evidence on which they are based.	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	
13. EXTERNAL REVIEW Report the methodology used to conduct the external review.	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings)	

	☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE Describe the procedure for updating the guideline.	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OF OPTIONS Describe the different options for managing the condition or health issue.	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	
17. IDENTIFIABLE KEY RECOMMENDATIONS Present the key recommendations so that they are easy to identify.	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION Describe the facilitators and barriers to the guideline's application.	☐ Types of facilitators and barriers that were considered ☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation)	

	☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS Provide advice and/or tools on how the recommendations can be applied in practice.	☐ Additional materials to support the implementation of the guideline in practice. For example: ☐ Guideline summary documents ☐ Links to check lists, algorithms ☐ Links to how-to manuals ☐ Solutions linked to barrier analysis (see Item 18) ☐ Tools to capitalize on guideline facilitators (see Item 18) ☐ Outcome of pilot test and lessons learned	
20. RESOURCE IMPLICATIONS Describe any potential resource implications of applying the recommendations.	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA Provide monitoring and/or auditing criteria to measure the	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations	

application of guideline recommendations.	☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY Report the funding body's influence on the content of the guideline.	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	
23. COMPETING INTERESTS Provide an explicit statement that all group members have declared whether they have any competing interests.	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	

Appendix Tables C2. The Conference on Guideline Standardization (COGS) checklist for reporting clinical practice guidelines

Topic	Topic Description	How Topic Addressed
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic, or therapeutic interventions that were considered during development.	
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	

8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, an expiration date for this version of the guideline.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength based on the criteria described in Topic 9.

15. Potential benefits and harms	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes.