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Clinical Practice Guidelines: Tools to Support High Quality Patient Care

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Clinical practice guidelines (CPGs) are systematically-developed statements aimed to assist decision-making relevant to the clinical encounter, to inform clinical policy, and to strengthen health care systems. The development of a CPG begins with the identification of a problem for which evidence-informed guidance is required. Interdisciplinary panels work to craft – and then execute - a protocol that will serve as a blueprint for the development process. It includes the scope of the project; who is involved and how they will function; the specific systematic review and consensus methods that will be used to ensure quality recommendations and to mitigate bias. CPGs should undergo a formal review of relevant stakeholders and results of this review, actions taken by the panel, and the final recommendations should be documented in the final CPG report. Dissemination activities, including the use of social media platforms, and more purposefully designed implementation activities are required to optimize the adoption of recommendations. Methods to keep recommendations current are required to ensure on-going validity and credibility of the recommendations. Two tools, AGREE II, and the AGREE REX, provide quality criteria related to the whole CPG development process and the CPG recommendations, respectively. The AGREE II is comprised of 23 items within 6 CPG quality domains: scope and purpose, stakeholder involvement, rigor, clarity of presentation, applicability, and editorial independence. The AGREE REX is comprised of 9 items within 3 CPG Recommendation quality domains: clinical applicability, values and preferences, and implementability. CPGs are important tools to an overall quality agenda.
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Clinical practice guidelines (CPGs) are systematically developed statements aimed to assist decision-making relevant to the clinical encounter, to inform clinical policy, and to strengthen health care systems.[1-2] High quality CPGs are informed by a systematic review of evidence, and an assessment of the benefits and harms of alternative care options. In this chapter, we will address the various uses of CPGs, provide a snap shot of the guideline development process, and describe features that define a high-quality CPG.

Roles of CPGs

CPGs contribute to an overall patient-centered quality agenda.[1-4] Through a systematic process of identifying, appraising, and synthesizing research studies, CPG developers make clear what published research is available to inform a particular clinical question or topic. CPG developers evaluate the research and interpret it within the clinical context where care is offered to make recommendations that can assist with decisions occurring in the clinical encounter. A CPG can address an array of clinical topics such as those that target public health, screening, treatment, diagnostic, or prognostic issues. In the field of nuclear medicine, several CPGs exist that target issues related to diagnosis of disease and therapeutic interventions.[5-6] For instance, Cancer Care

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Ontario's Program in Evidence-Based Care (PEBC) has provided guidance on the role of Gallium-68 PET imaging to diagnose adult patients with clinical and biochemical suspicion of neuroendocrine tumors[5] and has likewise provided recommendations on the use of on the use of Peptide Receptor Radionuclide Therapy and ^{131}I-Metaiodobenzylguanidine (MIGB) for the treatment of neuroendocrine tumors.[6]

Increasingly, CPG recommendations are also used to support clinical policy and health system design.[4-5] They also serve as part of the portfolio of information used by decisions-makers regarding what care options to fund in its primarily publicly-funded health care system. In this context CPGs have been used to inform decisions about continued funding for radionuclide treatment centers and in the prioritization of high-quality randomized controlled trials to develop the evidence base in the field.[6]

In addition, CPGs can reveal gaps in the primary research enterprise. For example, the search for studies may yield insufficient evidence or evidence of such poor quality that it becomes extremely challenging to make strong and definitive clinical recommendations. In these circumstances, CPG development groups may conclude that recommendations are not possible, make recommendations that certain clinical activities should be carried out in the context of a clinical trials program only, or offer conditional or temporary recommendations as the evidence-base continues to develop and mature.[2]

CPGs do not replace clinical decision-making; that has never been the aim of these tools. Instead, high quality CPG recommendations provide unbiased direction about health care options that are effective, safe, and appropriate to a defined patient population. CPGs can also provide recommendations about health care options that are not effective or may be potentially harmful and that should be avoided. However, the transferability and tailoring of recommended actions – that are based on population-level estimates of effectiveness - to the individual patient and his or her unique clinical circumstances and to the context in which care is offered, will always be required.[7]

Developing a CPG – a Snapshot

While the specifics may vary across CPG development programs, there are common and fundamental steps in the methods used to create CPGs (Fig. 1).[2,8,9]

Initiation

The CPG development process begins with one or more questions or problems for which evidence-informed advice is sought. For example, perhaps there is unexplained and concerning variation in practice of radionuclide therapy in the treatment of neuroendocrine cancers across jurisdictions. In response, a professional society may seek to reduce variation by developing evidence-informed recommended treatments that yield the most clinical benefit, avoid the greatest harms, and are safe and acceptable to patients and clinicians. Alternatively, perhaps there is a new radiotherapeutic pharmaceutical being released and the clinical community is seeking advice on its role relative to other treatment options.

Once a problem has been identified, a CPG panel is established. The CPG panel should be composed of a multidisciplinary team of clinicians, research methodologists, patients and family members, and other stakeholders, such as content stakeholders (eg, nuclear medicine physicians, technologists, chemists, and nurses). Issues of competing interests should be considered in the selection of participants.

Create a Draft CPG

Just as in the primary research enterprise, a formal protocol that reflects the operationalization of the steps listed below is required. It should be designed before the CPG development process begins. The protocol can serve as the blueprint to guide the development process.

The panel members refine the scope of the project, and determine the research questions and the methods that will be used. The methods include articulation of eligibility criteria that will be used to develop the evidence base following systematic review methods. Systematic reviews are described elsewhere in this issue and will not be repeated in detail here. For CPG development, rubrics (such as PICOT for treatment topics – see below) to create a researchable question to guide the systematic review process are very instrumental to focus the scope, mitigate potential bias, and to avoid project scope creep.

It is important to remember that the goal of developing a usable CPG is to choose evidence that will actually help to inform decisions. As a consequence, CPG developers are encouraged to be selective in choosing study design criteria (eg, clinical trials and comparative studies only), sample sizes, and outcomes that are clinically relevant and patient-focused and that address both the benefits, and harms of the care options being considered.

CPG panels need to choose and apply methods to judge the strength, quality and certainty in the body of evidence, and then use the evidence to inform the recommendation. In developing the recommendation, the evidence must be considered in the context of its relevance, its interface with the values and preferences of various stakeholders, and potential implementability of recommended care options. Recommendation statements should be actionable. Users should also have a clear understanding of the relative obligation or strength of the recommendation action.

Throughout the process, judgments are considered frequently. As a consequence, choosing methods by which consensus will be reached and having clear thresholds of consensus are important decisions the panel must make. Are recommendations only permissible when all members or how many members are in agreement? How will agreement be measured? While there is no one strategy to achieve consensus, it is important that the CPG development panel makes these decisions a priori and as part of their protocol.

There are excellent resources to direct the sections that should be included in a draft CPG document. These sections

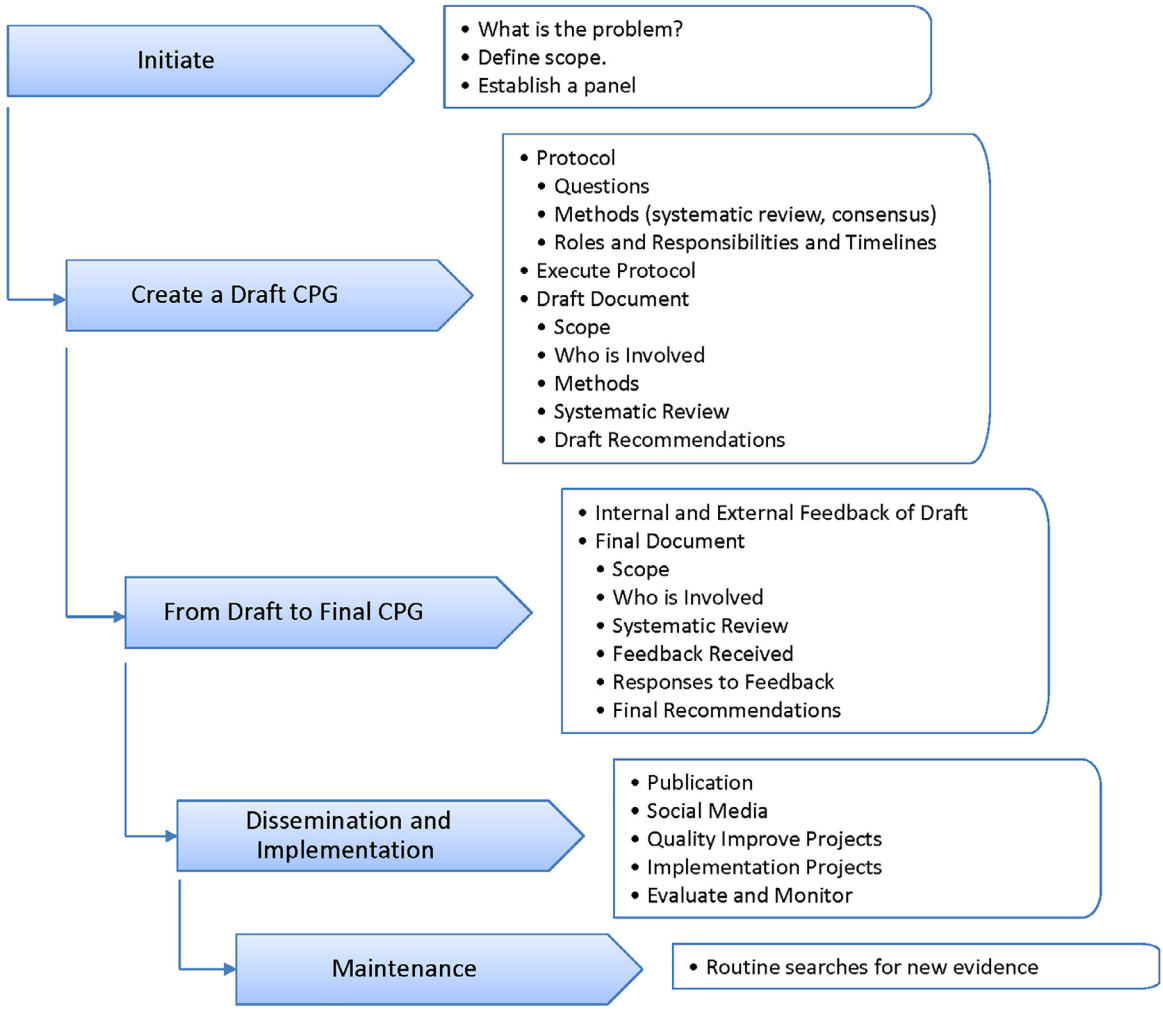

Figure 1 CPG Development Cycle. Fundamental Steps in the Methods Used to Create CPGs[2,8,9]

focus on scope, individuals involved, the systematic review of the evidence, and the draft recommendations.

From Draft to Final CPG

Once a CPG draft is completed, it needs to be vetted by relevant stakeholders. Often guideline programs have internal reviewer and external reviewers. The methods used to solicit feedback, the phenotype of reviewers, the feedback received, and responses to the feedback by the CPG panel should be reported in a transparent and explicit fashion in the final document or in accompanying documents.

Dissemination and Implementation

A dissemination plan and implementation plan for the CPG, ideally considered at the outset of the process, is the next step of the process. CPGs do not get used on their own. CPGs are an important part of a larger strategy to facilitate the adoption of recommendations. Public release of guidelines — through peer review journals, websites, and other social media platforms are typical dissemination strategies used once a CPG is complete. But building the recommendations into quality improvement initiatives, the design and execution of formal implementation plans, or integration into effective training and continuing education efforts are more opt to see success in the adoption of the evidence.

Maintenance

Once a CPG is completed, reviewed, disseminated, and implemented, it is not over. The CPG must be kept current and credible through routine monitoring of interpretation and integration of new evidence and updating of recommendations when required.

What Makes a High Quality CPG

The promise of CPGs is only as good as their quality. Poor quality CPGs can be biased and lead to recommendations that are of poor quality, not effective, potentially harmful, or difficult to implement. Considerable efforts by the health services research community have been directed towards mitigating the risk of poor-quality CPGs.[1,9-23] For example, the investigative teams of the AGREE Enterprise, an international program of CPG research, have used evidence-based methods to produce a collection of tools to support the

reliable and valid evaluation of CPGs and to support their development and reporting.[10-14,21] The AGREE II and the AGREE REX are two of the tools in the portfolio.

AGREE II and AGREE-REX Tools

The AGREE II is a reliable and valid CPG evaluation tool and a foundation upon which to direct CPG development and reporting (Table 1).[10-13,21] Comprising 23 items in 6 domains, the AGREE II targets the whole CPG development process — the "who," the "what," the "how," and the "where." AGREE II can be used to determine if a CPG or set of CPGs aligns with methodological quality expectations. Its reporting checklist format can also be used to guide development and reporting so that quality expectations are reflected in the document. Recognizing that even high quality methods may yield CPG recommendations in which their clinical relevance, acceptability, and implementability are not optimized led to the development of the AGREE-REX. The AGREE-REX focuses specifically on quality of the CPG recommendations (Table 2)[13,14,21] and be used to evaluate if they meet expectations for relevance, acceptability, and implementability or to inform development and reporting. The AGREE II and AGREE-REX are complementary resources.

Quality of Whole CPG: AGREE II

There are 6 thematic areas to consider in the AGREE II tool as domains when trying to optimize CPG methodological quality.[10-13,21]

Scope and Purpose

When evaluating the quality of a CPG, there should be a concise statement of its objectives, what specific health questions will be addressed, and the patient populations for whom it is meant to apply.

Objectives

This quality criteria deals with the potential health impact of the CPG. This could include impacts on patients or populations, on the health system, or society at large. Knowing the intent of the CPG, its potential for benefit (or to mitigate risks) and for whom or what enables readers to determine its relevance to their purpose.

Questions

A detailed description of the health questions covered by the CPG should be provided, particularly for the key recommendations. Rubrics exist to help ensure that all elements are

Table 1 Appraisal of Guidelines, Research, and Evaluation II (AGREE II) Domains and Items[21]

AGREE II Domain	AGREE II Item
Scope and purpose	1. The overall objective(s) of the CPG is (are) specifically described.
	2. The health question(s) covered by the CPG is (are) specifically described.
	3. The population (patients, public, etc.) to whom the CPG is meant to apply is specifically described.
Stakeholder involvement	4. The CPG development group includes individuals from all relevant professional groups.
	5. The views and preferences of the target population (patients, public, etc.) have been sought.
	6. The target users of the CPG are clearly defined.
Rigor of development	7. Systematic methods were used to search for evidence.
	8. The criteria for selecting the evidence are clearly described.
	9. The strengths and limitations of the body of evidence are clearly described.
	10. The methods for formulating the recommendations are clearly described.
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
	12. There is an explicit link between the recommendations and the supporting evidence.
	13. The CPG has been externally reviewed by experts prior to its publication.
	14. A procedure for updating the CPG is provided.
Clarity of presentation	15. The recommendations are specific and unambiguous.
	16. The different options for management of the condition or health issue are clearly presented.
	17. Key recommendations are easily identifiable.
Applicability	18. The CPG describes facilitators and barriers to its application.
	19. The CPG provides advice and/or tools on how the recommendations can be put into practice.
	20. The potential resource implications of applying the recommendations have been considered.
	21. The CPG presents monitoring and/or auditing criteria.
Editorial independence	22. The views of the funding body have not influenced the content of the CPG.
	23. Competing interests of CPG development group members have been recorded and addressed.

Abbreviation: CPGs, clinical practice guidelines.

Table 2 Appraisal of Guidelines, Research, and Evaluation Recommendation Excellence (AGREE-REX) Domains and Items[21]

AGREE-REX Domain	AGREE-REX Item
Clinical applicability	1. Evidence
	2. Relevance to target users
	3. Relevance to patients/ populations
Values and preferences	4. Values and preferences of target users
	5. Values and preferences of patients/populations
	6. Values and preferences of policy- and decision-makers
	7. Values and preferences of guideline developers
Implementability	8. Purpose
	9. Local applicability and adoption

included in a research question. In treatment research questions, "PICOT" and "PICOH" rubrics are often used to direct questions (Population, Intervention, Comparison, Outcome, and follow-up Time/Health care setting).[24] "PIRO" (Population, Index test, Reference standard, and Outcome) and "PFOT" (Population, prognostic or predictive Factor(s), Outcome, and follow-up Time) can be used to help define diagnostic and prognostic questions, respectively.[25,26]

Population

A clear description of the population (ie, patients, public, etc.) covered by a CPG should be provided. Information about the population should include gender and age, clinical condition, and if relevant severity/stage of disease, comorbidities, and related populations that are excluded.

Together, these quality criteria will enable the reader to determine whether to adopt the CPG to inform clinical practice or to inform clinical policy. It is important for clinicians to consider the scope and purpose criteria of a CPG to determine if the recommended clinical actions directly align with their scope of practice and also whether the CPG scope aligns with patient care elsewhere in the care trajectory. For example, the use of PET technology may be involved during the diagnostic, treatment, or surveillance phases of the cancer journey. Radiologists who have an understanding of the types of recommended care options across this journey and what specialists offer these care options can facilitate multidisciplinary discussions to ensure their patients receive appropriately timed and sequenced care for their PET procedures and the risks are mitigated.

Stakeholder Involvement

This quality domain focuses on who is involved in the development of the CPG, who is the CPG designed for, and how patients are involved in the development process.

Professional Involvement

These quality criteria refer to the professionals and content experts who were involved at some stage of the development process. The members of the CPG panel and information about the composition, discipline, and relevant expertise should be provided. A high-quality CPG panel that is multidisciplinary comprising clinicians, methodologists, and patients (see below) ensures appropriate methodological, content, and experiential perspectives are at the table and serves as one strategy to mitigate bias, enable debate, and the thoughtful contextualization of the evidence to inform the recommendations.

Patients and Populations

Information about target population values of health care should inform the development of CPGs. There are various methods for ensuring that these perspectives inform the different stages of CPG development by stakeholders. For example, some CPG initiatives include patient/public consultation groups who inform priority topics or outcomes or approve final recommendations.[6] Alternatively, information could be obtained from interviews of these stakeholders or from literature reviews of studies analyzing patient/public values, preferences, or experiences with the clinical condition of interest.[5] More and more, full integration of patients and public as active members of the CPG panel are the norm. There should be evidence that some process has taken place and that stakeholder's views have been considered in a high-quality CPG.

Target Users

The target users (eg, radiologists, family physicians, and administrators) and their role (eg, inform clinical decisions, inform to whom care should be referred to and when, and to inform funding decisions for radiopharmaceuticals) should be clearly defined in the CPG so the reader can immediately determine if the CPG is relevant to them. As with the rationale described in the scope and purpose above, CPG developers should consider target users to be not only as those who will execute the recommended clinical action but also those who see the patient somewhere along the care trajectory.

Rigor of Development

This quality theme is where the bulk of research in the CPG enterprise has focused, and it is often considered the most important one to achieve success.

Creating the Evidence Base: Searching, Selecting, and Appraising

The development of a systematic review as an evidentiary foundation is common in high-quality CPGs, as discussed elsewhere in this issue. In brief, details of the strategy used to search for evidence should be reported and include the search terms used, sources consulted, and dates of the literature covered. The selection criteria should be reported and should include information about the target population, study designs, the object of study (eg, treatment option and diagnostic procedure), comparison if relevant, and study outcomes.

The methods by which the risk of bias of individual studies is assessed and the body of evidence appraised should be described. For example, the widely used assessment tools of risk of bias for randomized controlled trials (RCTs) of intervention, nonrandomized comparative studies of intervention, diagnostic studies, and prognostic studies are the Cochrane Collaboration tool for RCTs,[27] ROBINS,[28] QUADUS-2,[29] and QUIPs,[30] respectively. This should also include any decision-rules or thresholds used to limit individual studies and assist in making recommendations. For providing an assessment of the entire body of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) strategies are popular methods used to operationalize various components of quality.[16,17,22]

Transparent, explicit, and reproducible methods to create the evidence base allow the reader to make judgments about the relevance of the evidence, the success of the CPG developers to mitigate bias, and to have confidence in the results. At the same time, from a CPG development perspective, rigorous, and transparent methods are critical to enable successful updating of the CPG as new evidence emerges. The parameters in the original search and selection can be maintained to ensure they are appropriate to integrate new data with the original.

Formulating Recommendations

A description of the methods used to formulate the recommendations and how final decisions were arrived at should be provided. The factors used to interpret the evidence, methods used to come to consensus, and thresholds for consensus should be included in the description. Important factors include values and preferences about candidate options, their acceptability, and their implementability in the context in which care is offered. There are useful methods to assist CPG developers in this process from moving from the evidence to recommendations, for example, the Evidence-to-Decision framework.[18]

While high quality study designs such as RCTs can make development of CPG recommendations more straightforward to write and make the confidence in the recommendations more certain, they are not required to create a CPG. CPGs informed by lower quality of evidence can still inform decision-making but the framing of recommendations should reflect a lower expectation of obligation.

Benefits, Risks, and Side Effects

The CPG should consider health benefits, side effects, and risks when formulating the recommendations. Outcomes may include survival, performance of a procedure, quality of life, adverse effects, and symptom management. There should be evidence that these issues have been addressed. For example, in the recent meta-analysis of 6 studies that were referenced earlier,[5] Ga-68 PET or PET-CT was shown to be highly sensitive (sensitivity = 91%, 95% confidence interval [CI], 85%-94%) and specific (specificity = 94%, 95% CI, 86%-98%) for evaluating patients with a suspicion of neuroendocrine tumors at initial diagnosis. However, Ga-68 PET or PET-CT is not perfect, resulting in some patients receiving false-positive or false-negative results. Patients with false-positive results may receive unnecessary treatment, and patients with false-negative results may not receive appropriate management. Thus, other disease-specific information (eg, ki-67 and differentiation) may need to be considered and obtained from a tissue biopsy if possible, as a strategy to mitigate these risks.

Link between Evidence and Recommendations

An explicit link between the recommendations and the evidence on which they are based should be present. The links may be reflected as reference lists appended to each recommendation or group of recommendation or a summary of the key evidence that underpins each recommendation. The CPG user should be able to identify the components of the body of evidence relevant to each recommendation.

External Review

All draft CPGs should undergo some sort of consultation process.[2,31] This external review step is important for several reasons. First, it provides an opportunity for new evidence to be identified that may have been inadvertently missed and for alternative valid interpretations to the evidence to be offered that may not have been considered by the panel. Second, it can serve as a dissemination strategy to enable stakeholders to know of impending changes to clinical practice and evidence about new care options. It also provides a means to democratize knowledge and create a level of accountability between panel members and their peers. This meaningful engagement with stakeholders can also serve as a lever to facilitate the ultimate adoption by the intended targets of the CPG recommendations. The CPG should report the purpose and intent of the external review, methods used in the external review (rating scales and structured questions), the phenotypes of stakeholders invited to review (numbers and disciplines), a summary of the external findings, and a response by the CPG panel to the feedback (how did the results influence the final recommendations).

Updating

Guidelines need to reflect current research. A formal process for updating the CPG describing the ideal timing, triggers for updates, and the methodology used to find and consider new evidence, should be described in the CPG document. The parameters in the original search and selection can be maintained to ensure it is appropriate to integrate new data with the old. There are useful resources to support updating processes, including the CHECK-UP toolkit and published updating procedures.[19,32,33]

Presentation

Presentation is not a quality dimension intended to make a CPG look pretty. It is intended to present the information and the recommendations in an easily identifiable, transparent, and explicit manner.

Specific, Unambiguous, and Identifiable Recommendations

Recommendations should be actionable statements. CPG users should know what action is being recommended, for what purpose, for which individuals, and how. Caveats or qualifying statements can provide the additional information required to appropriately contextualize the evidence.

There is debate about what to do in circumstances in which the evidence is not clear cut or there is uncertainty about the best option. Some CPG panels use language and labels to reflect the uncertainty (eg, "may be used" is a reasonable alternative) and other groups avoid the use of these terms — sometimes referring to them as weasel words. Strength of recommendation (strong recommendations versus weak or strong vs conditional recommendations) is often used. However, CPG users must not conflate different reasons why certain labels may be used (eg, one might be certain that the benefits only marginally outweigh the harms or that the evidence is not demonstrating consistency in results). Users should be able to find the most relevant recommendations easily. Document formatting techniques (bold, bulleted, italicized, colored, or inside boxes) can assist in providing clear visual clues.

Applicability

Facilitators and Barriers

There may be existing facilitators and barriers that will impact the adoption of CPG recommendations. These may be related to the recommendations themselves (eg, acceptability of recommended actions), the people involved (eg, skills of clinicians and adherence by patients), and organizational and system level issues (eg, funding of new technology and access to new health services). Understanding of these issues may result in modifications to recommendations to make them more actionable or suggestions for how issues might be addressed through an implementation plan. A high-quality CPG should identify relevant facilitators and barriers, how this information was gathered and their impact on the recommendations.[2]

Tools

CPG recommendations do not implement themselves. Tools to support action are a sign of a high-quality CPG.[34] Examples include a summary document, a quick reference guide, educational tools, results from a pilot test, patient leaflets, flow charts, check lists, or computer support platforms that initiate reminders.

Resources

The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialized staff, new equipment, and expensive drug treatment. A high-quality CPG should identify the types of cost information or costs analyses that were considered, methods by which the information was sought, what the information yielded, and the impact.

Audit

Measuring the application of CPG recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the CPG. The criteria may include process measures, behavioral measures, clinical, or health outcome measures.

Editorial Independence

Editorial independence from the funding body and being explicit about the competing interests of CPG authors are essential to maintaining the credibility of the document and reducing real or perceived conflicts.[35] Not only are most familiar financial competing interests important to consider but also intellectual, organizational, and even political interests can be important to document and manage. Also, once potential conflicts are identified, the CPG should also describe the strategies implemented to avoid or manage them.

Quality of the CPG Recommendations: AGREE REX

High quality recommendations are those that are clinically relevant, consider the values of various stakeholders, and are implementable.[13,14,21]

Clinical Relevance

Recommendations will be relevant if they address a clinical/health problem that is important to the target user (eg, physicians and nurses), provide actionable guidance appropriate to their scope of practice and the patients they see, and will result in clinical changes that are important to their patients.

Values and Preferences

Consideration of the values and preferences of different stakeholders is a defining feature of high quality recommendations. Stakeholders include a broad range of actors including target users (eg, nurses, physicians, and technicians), patients, policy makers, and the CPG developers themselves. For example, a patient's values and preferences can influence the acceptability of the recommended action. Where there is great variability in values and preferences, tools to support shared decision-making, such as decision aids, may be advised (2). Understanding CPG developer values provides users with information about the relative importance of different factors (eg, the priority of different outcomes) and how CPG developers managed conflicts when values did not align.

Implementability

Finally, the benefits of CPGs will only be realized if recommendations are put into practice. The implementability of CPG recommendations requires an alignment between the actual recommendations and the goal(s) of the CPG. For example, are the recommendations intended to be adopted immediately or

are they to be used to leverage clinical policy or funding decisions with the goal of eventual access to the care option? High quality CPGs includes tools to support the adoption of recommendations. Examples of effective implementation tactics include some types of educational strategies, building recommendations into electronic medical record systems, the use of audit and feedback strategies, client reminder systems or patient reminder systems, use of local champions, and development of clinical policies and performance management strategies.

CPGs have the capacity to improve health care outcomes, strengthen health care systems, and raise the bar with respect understand the strengths and limitations of evidence as part of the decision-making process. With the thoughtful application of rigorous process and engaged collaborators focused on a clear objective, research evidence can be integrated with clinical decision making to improve patient care and system effectiveness. In this article, key features of a robust CPG have been outlined to inform readers about what is required for their development and what to look for when using them.

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