MANUAL FOR CLINICAL PRACTICE GUIDELINE DEVELOPMENT

DEPARTMENT OF HEALTH-PHILIPPINES AND
PHILIPPINE HEALTH INSURANCE CORPORATION

First Edition 2018

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ACKNOWLEDGMENT

The Manual for Clinical Practice Guideline Development was initiated by the Department of Health – Health Policy Development and Planning Bureau, Disease Prevention and Control Bureau, Health Facility Development Bureau, and the Philippine Health Insurance Corporation. Grateful acknowledgement is hereby extended to all experts who participated in the focus group discussions and consultations and to Kalusugan ng Mag-Ina, Inc. and Asia Pacific Center for Evidence Based Healthcare, who provided technical assistance in drafting this manual.

PREFACE

This Manual supplements Administrative Order 2018-0019, which institutionalizes the Clinical Practice Guideline development in the country. It outlines the key processes in developing Clinical Practice Guidelines to standardize methods and assist CPG developers and program implementers in the country.

Suggested citation:
Department of Health Philippines. 2018. Manual for Clinical Practice Guideline Development.

MESSAGE FROM THE SECRETARY OF HEALTH

The revitalized Philippine health sector agenda, now called FOURmula One Plus (F1+), puts our people at the top of everything that we do in the DOH. Being the primary steward of the nation's health, we believe that our success can only be measured by the well-being of our fellow Filipinos and how well the health system responds to their needs.

The Fl+ strategy guarantees the provisions of and access to quality, effective, and safe healthcare services and health interventions. It stresses the need to enforce standards, to ensure accountability and transparency, and to advance quality. To improve the quality of clinical practice, medical professionals should be equipped with tools that will guide them in their decision-making. Clinical practice guidelines (CPGs) are the tools that help minimize inappropriate variations in clinical practice and improve the quality, effectiveness, efficiency, and safety of clinical decisions.

For a long time, the development of CPGs has been a collaborative effort between the Department of Health and medical societies. This manual introduces and captures the necessary steps to develop and evaluate CPGs. This is a timely aid to further improve the quality of CPGs, its dissemination and implementation as well as monitoring and evaluation.

It is my fervent hope that this manual will greatly assist health practitioners, clinicians, policymakers, academe, and civil societies and catalyze the attainment of Universal Health Coverage.

DR. FRANCISCO DUQUE III, MSc.
Secretary of Health

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LIST OF ABBREVIATIONS

AGREE	Appraisal of Guidelines for Research & Evaluation
CI	Confidence interval
COGS	Conference on Guideline Standardization
COI	Conflict of interest
CP	Consensus Panel
CPG	Clinical practice guideline
DCOI	Declaration of conflict of interest
DOH	Department of Health
ERE	Evidence Review Experts
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HTA	Health technology assessment
KM+	Knowledge Management Plus
NCP	National CPG Program
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QRP	Quality Review Panel (National Guideline Review Panel)
RCT	Randomized controlled trial
SDH	Social Determinants of Health
SR	Systematic review

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I. INTRODUCTION

CHAPTER ONE

CLINICAL PRACTICE GUIDELINES

DEFINITION

Clinical practice guidelines (CPGs) are "recommendations intended to optimize patient care that are informed by a systematic review (SR) of evidence and an assessment of the benefits and harms of alternative care options" [IOM 2011]. The ultimate goal of a CPG is to improve the quality of healthcare by reducing inappropriate variations in practice and ensuring more efficient use of limited resources [Dans AL, Dans LF, and Silvestre MA 2017].

On a daily basis, physicians in the country utilize CPGs to guide their decisions on the management of their patients. CPGs play a crucial role in the health of Filipinos. However, there has been disparity in methods employed to develop CPGs in the country, and, as other international models have shown, this may lead to grave consequences.

ROLE OF CPGS

Healthcare providers utilize the recommendations from CPGs pertaining to screening, diagnosis, management, or monitoring of clinical conditions to improve effectiveness and quality of care [Kredo T et al. 2016]. The increasing use of CPGs arises from the need to reduce unexplained variation in practice, to monitor inappropriate care, and to manage costs of health care [Shaneyfelt TM et al. 1999; Heffner JE 1998]. CPGs may also function as educational tools, promote rational allocation of resources, provide benchmarks for quality control or audit purposes, and set priorities for future research [Kredo T et al. 2016; Lim W et al. 2008; Siering U et al. 2013]. CPGs also offer the means to bridge the gaps between policy, best practice, local contexts, and patient preferences [Kredo T et al. 2016].

The scope of CPGs differs from that encompassed by health technology assessment (HTA), with which it is often times likened to. HTA is defined as "the systematic evaluation of properties, effects, and/or impacts of health technology to inform policy decision making" [DOH (AO 2016-0034) 2016]. The scope of HTA includes consequences of the application of health technologies or interventions (i.e., drugs, devices, procedures, and systems of organization and financing) within the health system and considers evidence regarding clinical effectiveness, safety, and cost effectiveness utilizing benefit-harm assessment, economic evaluation, as well as the evidence-based CPGs [Luce BR et al. 2010].

CHAPTER TWO

CPG DEVELOPMENT IN THE PHILIPPINES

SITUATIONAL ANALYSIS OF CPG DEVELOPMENT PROCESSES IN THE PHILIPPINES

Critical appraisal of 87 CPGs (1999 to December 2016) using an adapted Knowledge Management Plus (KM+) tool was undertaken to analyze the CPG development processes in the Philippines. This tool was developed through the Knowledge Management Program of the International Clinical Epidemiology Network, key informant interviews, and focus group discussions. The CPG development processes of the Philippines were compared with international models of best practices in CPG development [Imperial ML et al. 2017]. The situational analysis showed that the CPG development processes in the country were affected primarily by constraints in both human and financial resources with inadequate technical capacity and use of varied methodology, culminating in inconsistent quality of locally produced CPGs.

Local CPG developers have identified the Department of Health (DOH) as the ideal partner to support CPG development. Collaboration with the DOH and related institutions would significantly enhance the development process by enabling the setting of priorities and standard definitions, increasing multi-sectoral involvement, streamlining CPG development to lessen duplications, and reducing funding dependence from pharmaceutical companies, which might pose problems as conflicts of interest (COIs). To standardize the varied processes of CPG development, there is a need to develop a manual for CPG development, to build capacity of health professional and stakeholders, and to create the National Clinical Practice Guideline Program (NCP). These would enable prioritization, enhance CPG development process, and facilitate CPG utilization by health practitioners and policymakers.

THE DOH PROCESS

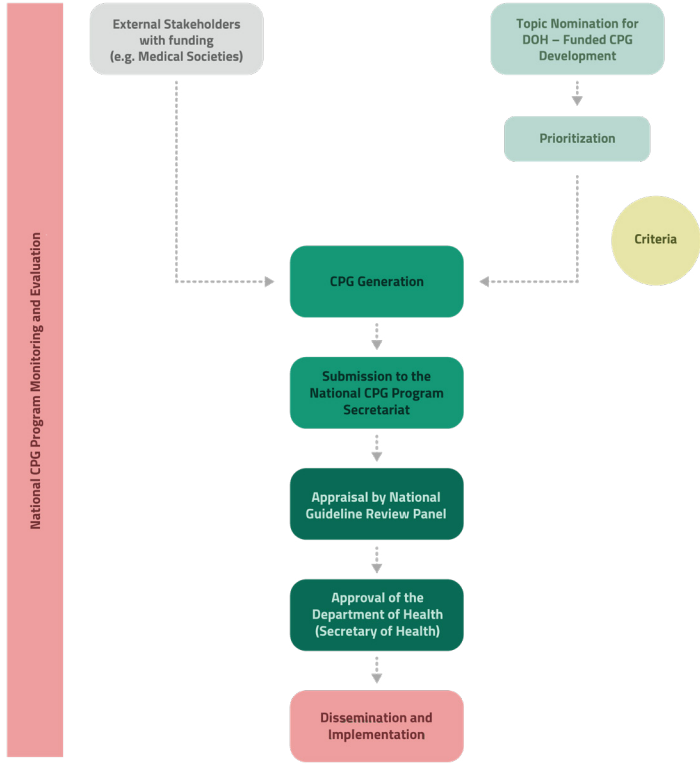
The CPG development process follows global standards with a few steps specifically adapted to the local setting. The diagram (Figure 1) depicts the steps which may be summarized in 4 phases:

1. Preparation and Prioritization
2. CPG Generation
3. CPG Appraisal
4. Implementation

Detailed roles on the development process will be discussed in succeeding chapters. Briefly, the process begins with stakeholders proposing topics of interest to DOH and DOH prioritizes the pipeline of CPGs it intends to finance. For each CPG, a Lead CPG Developer, who will manage all technical aspects of CPG development (e.g., convening working groups such as the Consensus Panel to identify important research questions), will be identified.

The completed manuscript will then be reviewed by a National Guideline Review Panel and then either be endorsed to Secretary of Health for approval as "National CPGs" or be returned to the Lead CPG Developer for revision. The NCP Secretariat oversees these steps and ensures that there is an implementation plan. Implementation encompasses dissemination, monitoring and evaluation, and other processes that key stakeholders and other third parties may be engaged to augment production, maximize distribution, increase awareness, and provide more effective assessment of CPG use. Extent of participation of various stakeholders is limited by the rules on the management of COI.

FIGURE 1. CLINICAL PRACTICE GUIDELINES DEVELOPMENT PROCESS



Source: AO 2018-0019: Guidelines on the Institutionalization and Implementation of the Clinical Practice Guideline Development

CHAPTER THREE

ROLES AND RESPONSIBILITIES OF STAKEHOLDERS

NATIONAL CPG PROGRAM SECRETARIAT

The NCP Secretariat will manage and ensure the implementation of the National CPG Program. They will provide technical and administrative support to the program such as facilitating the prioritization process for DOH-funded CPG development, convening of the quality reviewers, ensuring monitoring and evaluation of the NCP, and managing the storage of existing and completed CPGs.

The NCP Secretariat may engage an agency who will facilitate CPG Development. This may be an independent organization (i.e., an academic institution or other research organization) of professionals that has CPG development and research expertise, augmented by fundamental skills in project management, data handling and analysis, and medical writing.

The agency or institution shall demonstrate clinical and methodological expertise in the performance of tasks such as, but not limited to, the following:

1. Generating, conducting, and synthesizing research, resulting in the production of SRs, evidence reports, technical reports, technology assessments, and the like
2. Providing technical assistance to professional organizations, health agencies, healthcare providers, and policymakers to facilitate translation of the reports into CPGs, quality improvement tools, evidence-based curricula, coverage and reimbursement policies, and the like
3. Providing education and training in evidence-based practice for healthcare professionals

This agency is also responsible for the following tasks:

1. Provides administrative and technical support to the CPG development project
2. Engages additional content and technical experts as necessary
3. Collects, assesses, and manages conflicts of interests

NATIONAL GUIDELINE REVIEW PANEL

The National Guideline Review Panel (here on forth shall be called the Quality Review Panel or QRP) convened by the NCP Secretariat will appraise the completed CPGs. It will assure that all standards in CPG development are followed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool (Brouwers M et al. 2010).

The QRP shall be composed of:

1 DOH official
(program manager or his/her designated representative) from the appropriate division/agency that is directly involved with the CPG subject or condition

2 content experts

2 methodologists

LEAD CPG DEVELOPER

The Lead CPG Developer refers to the main person or group who will spearhead the development of a CPG for particular topic. The Lead CPG Developer may be a DOH Program Manager, content expert, methodologist, or a combination of the three. They must have relevant technical knowledge and experience on the topic and may be engaged separately for every project. They may be representatives from medical societies or other institutions. The Lead CPG Developer should be free from potential intellectual and financial COIs relevant to the contents of the CPG.

For each CPG to be developed, the Lead CPG Developer should perform the following tasks:

- Forms the CP and Evidence Review Experts (EREs)
- Drafts the scope and identifies the target audience of the CPG
- Develops and finalizes the Population, Intervention, Comparator, Outcome (PICO) clinical questions with the CP and EREs
- Develops CPG protocol, which includes the quality indicators to be used for monitoring and evaluating CPGs
- Submits CPG protocol to DOH for approval and implements it with ERE
- Approves the adaptation of existing CPG to be used, if applicable, and development of *de novo* evidence summaries
- Coordinates meetings with CP
- Coordinates the SR and evidence summaries with the EREs
- Designates a scientific writer from the EREs and oversees the writing and finalization of the CPG
- Sets expiration date and finalizes plans for updating CPG (together with ERE and CP)
- Submits the final CPG to DOH for external review and approval

II. PREPARATION AND PRIORITIZATION

CHAPTER FOUR

PLANNING THE CPG DEVELOPMENT

SELECTING THE TOPIC

The DOH facilitates topic selection for CPGs it will fund. Priority is given to topics that meet the following criteria: [Rosenfeld RM, Shiffman RN, and Robertson P 2012; Ministry of Health Malaysia and MaHTAS 2015]

TABLE 1. PRIORITIZATION CRITERIA FOR TOPIC SELECTION

1. Disease burden	Prevalence and/or incidence, comorbidity, morbidity and mortality, quality of life, and effectiveness of the preventive service on patients, their families, and communities
2. Public contention	Public interest surrounding the topic or disease condition
3. Cost-effectiveness	Result of an economic evaluation (e.g., cost-effectiveness analysis)
4. New evidence	Recent high quality evidence with potential to change previous recommendations
5. Potential impact	Potential to improve health outcomes and quality of life and/or decision-making resulting to practice change
6. Interest of public or care providers	Recommendations by practitioners or stakeholders
7. Variation in care	Potential to decrease variation in care (i.e., prevention, diagnosis, or treatment)
8. Sufficiency of evidence	Availability of clearly defined and high quality evidence
9. Timeliness	Urgency for guideline to be developed

Topic nominations and prioritization will be held twice a year; a contingency mechanism will also be in place to allow nominations for special contexts (e.g., public health emergencies). After the topic is approved and shortlisted, the DOH will initiate a process for contracting working groups for CPG development. Medical societies and other relevant stakeholders who can mobilize their own resources may opt to develop their own prioritization criteria.

PLANNING THE GUIDELINE DEVELOPMENT

There are many factors involved in the practical planning for developing a CPG, and the basic steps involved are as follows (adapted from the WHO Handbook for Guideline Development 2014):

1. Set objectives

It is important that the reason for embarking on the development of a CPG is clear to the group. Setting the objectives helps to determine the type of CPG that is needed and the timeline for the project.

A new CPG would be necessary given any of the following instances:

- when new evidence is published
- if the existing one lacks methodological rigor, casting doubt on the validity of its recommendations
- if there are observed differences in the characteristics of the patient population or the epidemiology of the disease condition
- if there is limited applicability of the existing recommendations in the area of practice
- if there are varying aspects of the disease in different areas such that the recommendations cannot be generalized
- when there is a wide variation in practice
- when there is underuse or overuse of a health technology such that its current use is not supported by clinical evidence.

2. Determine the scope

The scope of the CPG, which clarifies the characteristics of the topic, is laid out at the beginning of its development. The scope should briefly include the following: [WHO 2014; Minds 2014; NICE 2014]

a. Clinical characteristics of the disease condition
b. Epidemiology of the disease condition
c. Area of practice or policy where it applies
d. Population affected by the recommendations
e. The actions or interventions, settings, and expected outcomes
f. Economic perspectives

3. Identify the target audience

It is possible that a CPG may not meet the requirements of all users. The needs of a clinician will differ from that of a program manager or a user engaged in policy making, health financing, or standards accreditation. The key target audience should be identified to ensure that the CPG to be developed can effectively address the specific topic at hand (e.g., the clinical problems, the intended care or consumers/users, the settings where it will be applied, and interventions to be evaluated). Guideline recommendations will depend on the target audience.

4. **Identify and prioritize clinical questions**
   Key clinical issues should be identified, and from these, relevant clinical questions can be generated. The clinical questions are prioritized, and these would provide the direction for the literature search and synthesis that would follow. This would be further discussed in Chapter 7 Formulating Clinical Questions.

5. **Identify Stakeholders**
   Different problems and disease conditions would necessarily involve experts and stakeholders from different fields and disciplines. Individuals and experts from diverse groups or organizations relevant to the topic, including patients and patient advocate groups, should be invited to actively take part in formulating questions, drafting recommendations, and reviewing the CPG.

6. **Setting up the working groups**
   It is the responsibility of the Lead CPG Developer to identify and gather members of the different working groups that will take part in the CPG development. These working groups include the EREs that retrieve and synthesize evidence and the CP that votes on the recommendations. Group compositions and functions will be discussed in detail in Chapter 5 Setting Up Working Groups.

7. **Set the timeline**
   On the average, a CPG takes at least 6 months to 1 year to be completed. This would depend on the availability of financial and human resources. If the CPG is meant to address an urgent public health crisis, then a consensus statement or a rapid advice guideline would be more appropriate. Rapid advice guidelines are typically released in only a few months. The duration is highly dependent on the breadth of the scope and the volume of evidence supporting it. A CPG tackling more questions would understandably multiply the time and resource requirements, thus lengthening the duration of the process. Having methodology experts (e.g., ERE) on board would likely bring down the duration to an average of 6 months. Aside from allotting time for tasks, such as the literature search and drafting of recommendations, the timeline should include arranging dates for meetings and conferences, with advanced notice disseminated to members invited to be part of the committees.

8. **Propose a budget**
   The budget for the CPG and its development covers the costs of acquisition of journals, meetings and conferences, and possibly outsourcing a wide range of services from technical experts, medical writers, lay-out artists, and the like. Publication and dissemination also entails a significant portion of the funding. It is important that sources of funding are properly identified, approved, and documented prior to the project.

Aside from the planning stage, all the different steps of the CPG development process should then be incorporated and described in the protocol (Appendix A).

The succeeding chapters will describe the steps in summarizing the evidence, translating the evidence into recommendations, and implementing the CPG. The CPG protocol is the planning document that ensures that the CPG is focused and can be feasibly undertaken. The Lead CPG Developers then submits a completed protocol to the DOH for approval.

CHAPTER FIVE

SETTING UP WORKING GROUPS

There are different types of committees involved in the CPG development process, and their exact composition would depend on the topic. Group members are chosen based on their knowledge and experience, which may include any of the following:

1. **Practitioners** - specialists and generalists, primary care physicians, nurses and pharmacists, and/or academics
2. **Other relevant health professionals**
3. **Guideline implementers, program managers, and policy makers**
4. **Lay people** - patients and their families, caregivers, and other members of the community who use health services
5. **Methodologists** – clinical epidemiologists and experts in other disciplines (e.g., evidence-based medicine, health economics, biostatistics, and health social science) who are skilled in research methods, evidence synthesis, and guideline development

The multidisciplinary membership is critical to avoid bias and to give different perspectives in the CPG development. All members should be screened for possible COIs. An effective policy on COI should require:

- CPG development group members to disclose all potential COIs;
- that the chair and majority of CPG development group members be free of financial COIs;
- disclosure of all potential COIs of expert reviewers or advisers who are not officially part of the development group; and
- prohibit direct company support for CPG development, printing, or publication. This will be explained further in Chapter 6 Conflicts of Interest.

EVIDENCE REVIEW EXPERTS

The EREs, convened by the Lead CPG Developer, are tasked with reviewing existing CPGs, creating the evidence summaries, and drafting evidence-based recommendations. The EREs should have a general declaration of COIs and should be free of intellectual and financial COIs.

Composition (at least one each of the following, depending on the PICO questions and timeline):

- CPG/GRADE methodologist (see Chapter 11: Assessing the Evidence)
- Clinical epidemiologists or evidence-based practitioners
- Biostatistician
- Others (optional) - economist, information specialists, SRs, medical writers, editors

Roles:

- Develop the PICO questions in coordination with the Lead CPG developers
- Identify, review, and summarize existing CPGs and evaluate them for possible adaptation
- Identify relevant literature to answer the PICO questions and create a database to manage search results and strategies
- Critically appraise the evidence and create evidence summaries
- Formulate draft recommendations
- Prepare the presentation of evidence summaries during the CP meeting
- Document the development process and finalize CPG documents, which include the following:
    1. a detailed full-text CPG,
    2. a quick reference guide or abbreviated pocket guide, and
    3. a brief layman's version for the public
- Set expiration date and finalize plans for updating CPG (together with Lead CPG developers and CP)

CONSENSUS PANEL

Membership of the CP is dependent on the topic of the CPG. Members should be free of potential intellectual and financial COIs relevant to the contents of the CPG. Aside from content and methodology experts, other key stakeholders may be invited to join the CP. These would include patient advocates, health and social care practitioners, other professionals whose practice may be affected by the guideline or who can influence uptake of the CPG recommendations, public sector providers and commissioners of care or services, private sector, voluntary sector, and other independent providers of care or services.

Composition (10-15 people): Multi-sectoral representatives

- Health care practitioners such as specialists and primary care providers
- Patients or patient advocates (at least 1 representative)
- Methodologists (at least 1 representative) such as evidence-based practitioners, clinical epidemiologists, and economists
- DOH program manager (at least 1 representative)

Roles:

- Submits suggested PICO questions to Lead CPG Developers
- Prioritizes the critical and important outcome measures prior to finalizing the PICO questions, such that stakeholders' values and preferences can be incorporated
- Reviews evidence summaries and drafts recommendations prior to an *en banc* CP meeting
- Votes on the recommendations of the CPG during the *en banc* CP meeting
- Participates in a modified Delphi activity if no consensus is reached during the *en banc* meeting

CHAPTER SIX

CONFLICTS OF INTEREST

Conflicts of interest may be defined as a "set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest" [Lo B and Field MJ 2009]. COIs or competing interests have the potential to affect an individual's objectivity and independence. This may introduce bias in decision making.

TYPES OF COI

Financial - may relate to commercial or non-commercial interests. Examples of direct commercial COIs include employment, consultancies, stock ownership, honoraria, gifts, paid expert testimony, membership on "speakers' bureaus", patents or patent applications, and industry sponsored research or travel for the participant or family members. Non-commercial COIs include research grants and support from governments, foundations, or non-profit organizations, economic relations with specific companies or groups, and acquisition of research funds.

Intellectual or academic - occurs when a person or a professional group is jeopardized or enhanced by a guideline recommendation. Guyatt defined this as "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation" [Guyatt G et al. 2010]. Examples include having published a scientific paper on the topic, having received grant support related to the guideline, having personal beliefs related to the topic that may lead to biased writing and publishing, being a chair or member of another guideline committee relevant to the topic, involvement in an advocacy group that stands to benefit from recommendations, being a member of a lobbying or advocacy organization related to the topic, or having family members with the condition addressed by the CPG.

DISCLOSURE OF COI

All potential members must declare any conflict of interest before their participation, or during CPG development if any change occurs. A member should fill in a declaration of conflict of interests (DCOI) form (Annex B) and agree to its publication, especially those involved with the tasks of preparing SRs, contributing to the formulation of recommendations, and/or writing the CPG. The member is typically asked to disclose potential COIs that have existed in the 4 years preceding his/her involvement in the CPG development project.

ASSESSMENT AND MANAGEMENT OF COI

Having a COI or competing interest does not necessarily disqualify someone from participating in a CPG development group or as ERE. A declaration of COI will help avoid potentially compromising situations that could undermine or otherwise affect the work done. An administrative officer or staff designated by the NCP Secretariat to screen and manage COIs should collect all the DCOIs, review all COIs, and recommends to the Lead CPG developers the extent of participation that can be allowed. All DCOIs and their corresponding management must be reported and published with the CPG. In case where serious COIs are present, the member will have to be excluded from the project (see Table 2).

The management of the COIs is dependent on the magnitude of the declared financial or intellectual COIs:

- COIs that are not that significant may only warrant a DCOI at the meetings and be documented in the final CPG report.
- COIs involving personal or family ties with the company that manufactures a product or technology that may be recommended for use in the CPG; having received funding or compensation from the company that has interest
- Significant personal financial COIs in a company with a commercial interest in the outcome of the CPG as declared by a member will prevent his participation in the CPG development.

TABLE 2. MANAGEMENT OF CONFLICT OF INTEREST

CONFLICT OF INTEREST	EXAMPLES	POLICY ON HOW TO MANAGE COI
PRIMARY	▪ Monetary relations with company within last 48 months; includes spouse (financial) ▪ Authorship in papers with direct bearing on PICO question (intellectual)	▪ Cannot be part of the Lead CPG Developers, or members of the Evidence Review Experts, Consensus Panel, Quality Review Panel, but ▪ May participate in the discussion of evidence, e.g. with the Evidence Review Experts
SECONDARY	▪ Monetary relations with company, but covering interventions (e.g. drugs, in other areas) (financial) ▪ Authorship in reviews or other related CPGs (intellectual)	▪ May participate in the entire CPG development process but must declare COI
NONE	▪ None of the above	▪ May be involved in all activities in the CPG development process

COI=conflict of interest; CP=Consensus Panel; CPG=clinical practice guideline; PICO=Population, Intervention, Comparator, Outcome.

Existing DOH policies and guidelines on the declaration and management of COIs that are applicable for the NCP should supersede any COI guideline in this manual.

SUGGESTED READING

1. IOM (Institute of Medicine). 2009. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: The National Academies Press.
2. Boyd EA et al. Guideline Funding and Conflicts of Interest. Article 4 in Integrating and Coordinating Efforts in COPD Guideline Development. An Official ATS/ERS Workshop Report. Proc Am Thorac Soc Vol 9, Iss. 5, pp 234–242, Dec 15, 2012
3. Schünemann HJ. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. Ann Intern Med. 2015;163:548-553. doi:10.7326/M14-1885
4. World Health Organization. WHO Handbook for guideline development 2ed. 2014.

III. CPG GENERATION

CHAPTER SEVEN

FORMULATING CLINICAL QUESTIONS

It is important to choose the right questions based on the key clinical issues identified in the scope of the topic. Clear and focused questions will steer the evidence search and guide the development of recommendations. The number of questions depends on the topic, and it should be limited to a manageable number that can be suitably covered over the time and by the resources allocated for the project.

Clinical questions can either be one of the following:

1. background questions on definitions, disease prevalence, or pathophysiology or
2. foreground questions pertaining to the effectiveness, efficacy, or cost effectiveness of interventions and other outcomes such as social acceptability, preferences, and implications of the recommendation.

The latter will require an SR, since the answers to these questions will form the evidence from which recommendations to be made are based upon. Questions may also be broad or narrow in scope. Broad questions may have a larger body of evidence that will be more generalizable, while a narrow question might have less evidence and be less generalizable. A broad question will require more resources to answer, thus sometimes it is broken down into several narrow questions.

PICO FORMAT

The PICO format is used to frame a good clinical question. Its components are as follows:

P - patients, problem, population -characteristics of the patient (e.g., age groups, sex, ethnicity, social identities, behavioral characteristics, etc.), disease condition, setting, or other specific constraints

I - intervention - also designated as the exposure (E) of interest that the person experiences (e.g., therapy, procedure, diagnostic test, prognostic or risk factor, screening test, or preventive measure) and variations to consider (dosage, frequency, delivery or administration, personnel and delivery channels, timing and duration, etc.)

C - co-intervention, comparator, controls - the alternative choices of action (e.g., placebo, no intervention, standard of care or gold standard in diagnosis, or other variations of intervention)

O - outcome -measurable clinical/epidemiological/health outcomes relevant to the intervention/population, which includes, but is not limited to, efficacy, effectiveness, safety, adverse events, compliance, etc.

The clinical questions are also determined by the nature of the clinical issue being addressed, and different types of clinical questions may relate to the following (Table 3). In a single study, several Ps, Es and Os may be compared at the same time [WHO 2014]:

- **Treatment** - intervention efficacy and effectiveness
- **Harm** - unwanted risks and adverse events directly caused by or associated with the intervention
- **Diagnosis** - diagnostic approaches and test characteristics
- **Prognosis** - risk assessment including baseline risk and additional risk from a given exposure
- **Values and preferences of the individuals affected by an intervention**
- **Resource considerations** - including cost and measures of economic efficiency such as cost effectiveness

TABLE 3. APPROACH TO FORMULATING THE PICO QUESTION

TYPE OF QUESTION	SYNTAX	SAMPLE QUESTION
Therapy	Among P (patients with a certain disease), how effective is E (a certain treatment) in preventing O (an adverse outcome)?	Among children with human immunodeficiency virus (P), how effective is isoniazid prophylaxis (E) in preventing tuberculosis (O)?
Diagnosis	Among P (patients with a certain condition), how accurate is E (a certain test), in diagnosing O (a disease)?	Among patients with acute chest pain (P), how accurate is an electrocardiogram (E) in diagnosing acute myocardial infarction (O)?
Harm	Among P (patients with a certain condition), by how much does E (a potentially harmful exposure), increase the risk of O (an adverse outcome)?	Among healthy males (P), by how much does smoking (E) increase the risk of lung cancer (O)?
Prognosis	Among P (patients with a certain disease) who have E (certain prognostic factors), what is the probability of O (an outcome)?	Among patients with prostatic cancer (P) who have lumbar metastasis (E), what is the probability of death in the next 5 years (O)?

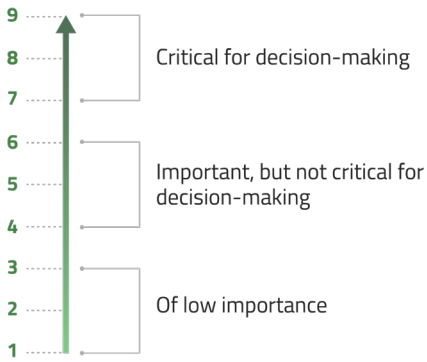
P = the population of interest; E = the exposure or intervention being evaluated; O = the positive or negative outcome (e.g. disease, complication or some measure of health).

Source: Painless Evidence-based Medicine. 2nd ed. Wiley-Blackwell, 2017

RATING OUTCOMES

Outcomes identified must be evaluated and ranked according to importance. These key outcomes will be considered when the CPG recommendations are drafted. Scoring is subjective and may be based on the CP's experience as well as the patient's views. A formal rating process is illustrated below, where outcomes are scored from 1 to 9 with increasing importance for decision making. "Important" and "critical" outcomes will affect guideline recommendations, while outcomes of "low or limited importance" will usually not have any bearing on the recommendations [GRADE Handbook 2013]. Firstly, the CP should decide if the benefits and harms of an intervention are important or not to the decision to be made on the management. Secondly, it should decide if that specific outcome is either critical to the decision or only important but not critical. Only important and critical outcomes are selected for actual SR. Outcomes of low importance are not included in the evidence profile. The outcomes are ranked by the CP members prior to finalization of the clinical questions.

FIGURE 2. GRADE SCALE FOR RATING OUTCOMES



Source: WHO Handbook for Guideline Development 2014.

The PICO questions are forwarded to the CP for any input from all relevant stakeholders. This will allow them to make revisions or include any omissions. PICO questions will be finalized by the Lead CPG Developers, and they will identify which questions would need SRs. This is an important step where the patient's values and preferences are incorporated in the recommendation and decision making.

SUGGESTED READING

1. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html

CHAPTER EIGHT

INCORPORATING EQUITY

The World Health Organization has emphasized that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition" [WHO 2006]. It has issued the call for all guideline developers to take equity, human rights, gender, and other social determinants of health (SDH) into consideration when they developed recommendations to reduce health inequities. The WHO has proposed 8 entry points for these in the CPG (Table 4). Similarly, a 4-part series in the Journal of Clinical Epidemiology gave detailed guidance on how health equity considerations should be incorporated in the guideline development process [GRADE equity series JCE 2017].

Incorporation of equity, human rights, gender, and the SDH should be considered at all phases of CPG development, from the planning stage, then all throughout the development process, culminating in the publishing and updating of the CPG. Assessment of equity considerations in the completed CPG are incorporated in the Equity Lens of the Knowledge Management Plus (KM+) tool. (Appendix B)

TABLE 4. INCORPORATION OF EQUITY, HUMAN RIGHTS, GENDER, AND THE SOCIAL DETERMINANTS OF HEALTH IN THE GUIDELINE DEVELOPMENT PROCESS.

STEP	RECOMMENDATIONS
Topic selection	Stakeholders may request that equity, human rights, and gender to be addressed during CPG development.
Planning the CPG	Planned outcomes should include how health is distributed within populations and across groups.
Setting up groups	Members who understand how to take equity, human rights, and gender into account and have the expertise to promote better health may be included. Representatives from marginalized groups may also participate in the CPG development process.
COI	Attention should be given to COIs that can lead to a weakened stance on equity, human rights, gender, and social determinants in the final CPG.

Formulating questions	Clinical questions addressing average effects resulting from an intervention and the distribution of effects across subpopulations; specific human rights and other issues related to laws, policies, standards, protocols, and guidelines; questions on effectiveness of interventions should consider the potential for differences in uptake and benefits as a function of social position.
Evidence retrieval and synthesis	Qualitative SRs should be used to retrieve, synthesize, and incorporate evidence on equity.
Evidence assessment	Quality assessment on equity, human rights, and gender of the evidence should be done.
Developing recommendations	If the intervention reduces health inequities, a strong recommendation will be made. However, if effect is not significant, a conditional recommendation is more appropriate.
Publishing and updating	CPG messages on equity, human rights, and gender (in terms of language, photographs, translations) must be clearly stated.
Adaptation, implementation, and evaluation	Clear references to health equity, gender, equality, and other relevant international human rights standards and principles should be included in the sections on implementation, monitoring, and evaluation

COI = conflicts of interest; CPG = clinical practice guideline; SDH = social determinants of health; SR = systematic review.

Source: WHO Handbook on Guideline Development 2014

GRADE EQUITY GUIDELINES

To address health equity issues in guideline development, disadvantaged populations or subgroups should be identified [Welch VA et al. 2017]. Inequity can be found in the following areas (PROGRESS-Plus):

P - place of residence

R - race/ethnicity/ culture/language

O - occupation

G - gender/sex

R - religion

E - education

S - socioeconomic status

S - social capital

"Plus" - other relevant characteristics such as age, disability, sexual orientation, time-dependent situations, and relationships.

CPGs should guarantee that their recommendations do not aggravate the conditions in these already disadvantaged groups.

CHAPTER NINE

SEARCHING FOR AND ADAPTATION OF EXISTING CPGs

EVALUATION FOR ADAPTATION

CPG development is a laborious, time-consuming, and costly undertaking. This may not be necessary if there is an existing international CPG on the same topic that can be modified to fit the local setting. CPGs may be adapted to address issues such as cultural differences, resource constraints, or end-user involvement [Groot P, Hommersom A, and Lucas P 2008].

A methodology to identify CPGs for adaptation was developed by the ADAPTE collaboration, an international group composed of researchers, guideline developers, and guideline implementers. They have proposed ADAPTE [The ADAPTE Collaboration 2009] as a systematic approach to modify CPGs produced in one setting to be applied and implemented in another context (Appendix C).

According to ADAPTE, the two key elements in the adaptation process are as follows:

1. transparent and explicit process with sufficient detail in the methods
2. appropriate referencing and acknowledgment to source documents.

Existing guidelines are systematically retrieved, and their quality and validity are assessed using the AGREE II tool (Annex C). This instrument is an internationally recognized assessment tool developed by the AGREE II Next Steps Consortium [Brouwers M et al. 2010]. The AGREE II tool assesses the quality of the CPGs based on their description with focus on the CPG development process. This tool consists of:

- Scope and Purpose (items 1–3)
- Stakeholder Involvement (items 4–6)
- Rigor of Development (items 7–14)
- Clarity of Presentation (items 15–17)
- Applicability (items 18–21)
- Editorial Independence (items 22–23)
- Overall Guideline Assessment (items 24–25)

The recommended cut off for a CPG to be considered trustworthy and of good quality is an overall score of 75% with no domain garnering a score lower than 75%.

Based on the appraisal results, the decision is made to adapt the trustworthy and well-done guidelines. The evidence summaries of the existing guidelines are matched to the specific PICO questions identified by the Lead CPG Developers. These evidence summaries may be used as the evidence base during the consensus building to finalize the recommendations.

LITERATURE SEARCH AND RETRIEVAL

The validity of a CPG primarily rests on the quality of the evidence that was reviewed and considered in the recommendations. A comprehensive search for SRs that covers all the relevant studies can be done by using well-formulated PICO clinical questions about interventions or exposures to be recommended (or not recommended) in the CPG. An SR allows the synthesis of a multitude of research with similar study designs that reduces the risk of citation bias, leading to more accurate and reliable decision making. It facilitates CPG development because it synthesizes the evidence and packages it in a format that is readily usable by the working group.

The search for original research is oftentimes laborious and time intensive. There are many sources that offer what is termed as "secondary literature", which is synthesized and evaluated evidence in the form of SRs, meta-analyses, guidelines, and critically appraised topics. It is possible that the ongoing literature search will yield published high-quality SRs or CPGs that are already available. In this situation, it is not mandatory to undertake an SR *de novo*, but instead efforts can be directed to appraising the existing SR and updating it accordingly.

CHAPTER TEN

SYSTEMATIC REVIEW

The SR for a CPG evaluates the strength of the body of evidence and provides a summary of the body of evidence using single or unified statements to help formulate recommendations.

SEARCH PROTOCOL

A search protocol is influenced by the type of evidence needed for the PICO clinical question. It will direct the search toward appropriate sources based on the eligibility criteria of the PICO clinical question and should be established before the search begins. A meticulous search strategy should cover a wide range of sources and may involve a step-wise approach as follows:

1. Identify study designs to be included, based on the available evidence or the PICO question
2. Identify supplementary literature - supplementary search techniques include forward and backward citation searching, journal hand-searches, or communication with experts and other stakeholders
3. Identify gray literature - literature not found in books or databases, and includes conference proceedings and theses, technical and research reports, government publications, policy papers, annual reports, fact sheets, maps, geological surveys, and statistics
4. Identify limits and filters applied - including language restrictions, time periods, age groups, human versus animal studies

SEARCH STRATEGY

There should be a structured approach to conducting a search. It can start with identification of the concepts involved by using PICO, then applying a methodology filter (e.g. RCT) to focus on the study design. These concepts may be prioritized according to importance, and search terms may be expanded or intersected until the search is narrowed down to a manageable number of articles. The search terms used may be subject index headings in the database plus key words in the title and abstracts of the studies.

The search strategy and conduct of the search done (including databases searched) should also be duly documented to allow replication by other researchers. Details to be recorded are sources searched, date search was conducted, period searched, subject headings and keywords used, search history, and results retrieved. The selection process and the resulting yield can be arranged in a flow diagram following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (PRISMA Group, 2009); this diagram should be included in the guideline (Appendix D).

REVIEW OF EXISTING SYSTEMATIC REVIEWS

A 2-step review process is used to identify relevant articles. First, citations unrelated to the topic may be excluded based on the titles and abstracts obtained. Second, the remaining titles and abstracts are then examined in accordance with pre-specified inclusion and exclusion criteria. Full-text articles are retrieved and reviewed accordingly. Additional literature citations may be gleaned from the references mentioned in review articles used.

There may be instances wherein there are already published SRs for the PICO questions. In this case, the existing SR may be evaluated to determine if it can be used instead of performing a *de novo* SR. Key elements are considered when assessing the quality of the SRs. The judgment on the quality depends on the presence of a combination of the following indicators:

1. a specific and clearly focused PICO Question that will form the basis for the pre-specified eligibility criteria
2. an explicit, reproducible strategy that facilitates a comprehensive, exhaustive, and systematic search for original articles and other information sources
3. a study selection and data extraction - done independently by at least 2 reviewers
4. a critical appraisal of the studies and an assessment of the risk of bias was done
5. a systematic synthesis, reporting, and presentation of the characteristics and findings of the included studies and the pooled results, if any

Specific questions addressing the above may be found in the guide to the appraisal of an SR in Annex D.

Based on the above parameters, the quality of existing reviews can be assessed, and the most appropriate ones can be chosen for the PICO question. It is also important to appraise new studies that were not included yet in the SR to determine if the results may be altered by the latest evidence. All these factors form part of the process to decide if the SR should be revised or updated or if there is a need to do a new review (Figure 3).

CRITICAL APPRAISAL

For *de novo* SR, the next step will be the critical appraisal of individual articles for their quality once full-text articles have been retrieved. Aspects of the study that will be evaluated are its directness, validity, results, applicability, and individualization of the results [Dans AL, Dans LF and Silvestre MA 2017]. Appraisal tools will help in assessing validity of the methodology used in each study. Specific forms (Annexes E-H) for the appraisal of studies on therapy, diagnosis, harm, and prognosis are available.

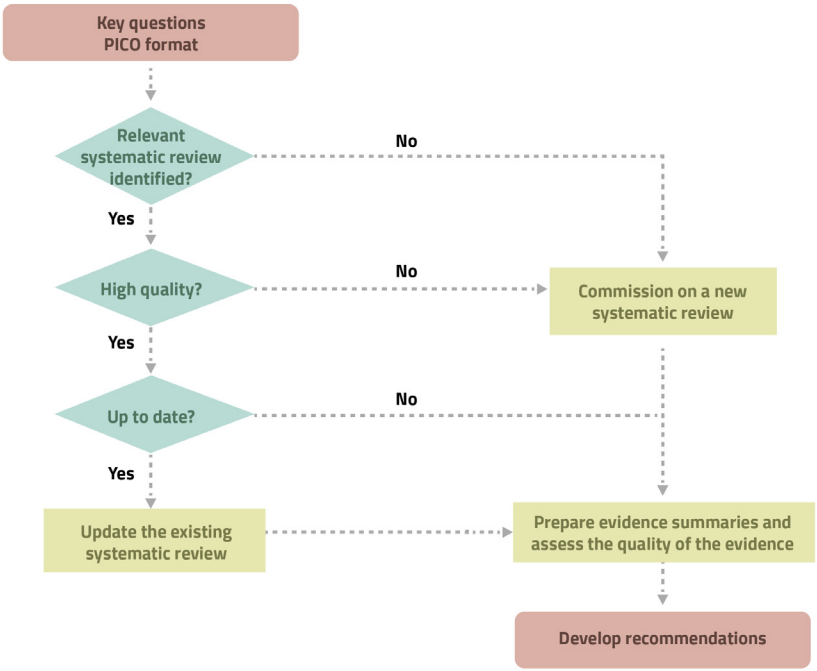
SYNTHESIS OF EVIDENCE

When the studies and results cannot be combined, a narrative summary of the individual studies in the review can be done with the results assembled in a table. The information in the table includes a brief description of the study design, methodology, population, setting, and research questions or outcomes for all relevant studies. The summary of the key findings containing included and excluded studies, clinical profiles, and total number of subject should be presented in the report. Additionally, a description of the methods used to compare interventions and comparators and to evaluate the risk of bias of each article. A conclusion statement should include a short discussion and few evidence statements [NICE 2014].

A meta-analysis is an evaluation undertaken by doing a statistical and quantitative integration of values of effect measures. This is done when selected studies exhibit a high level of homogeniety.

The SR for a CPG evaluates the strength of the body of evidence and provides a summary of the body of evidence using single or unified statements to help formulate recommendations.

FIGURE 3. PROCESS FLOW FOR USE OF EXISTING SYSTEMATIC REVIEWS



Source: WHO Handbook for Guideline Development 2014.

CHAPTER ELEVEN

ASSESSING THE EVIDENCE

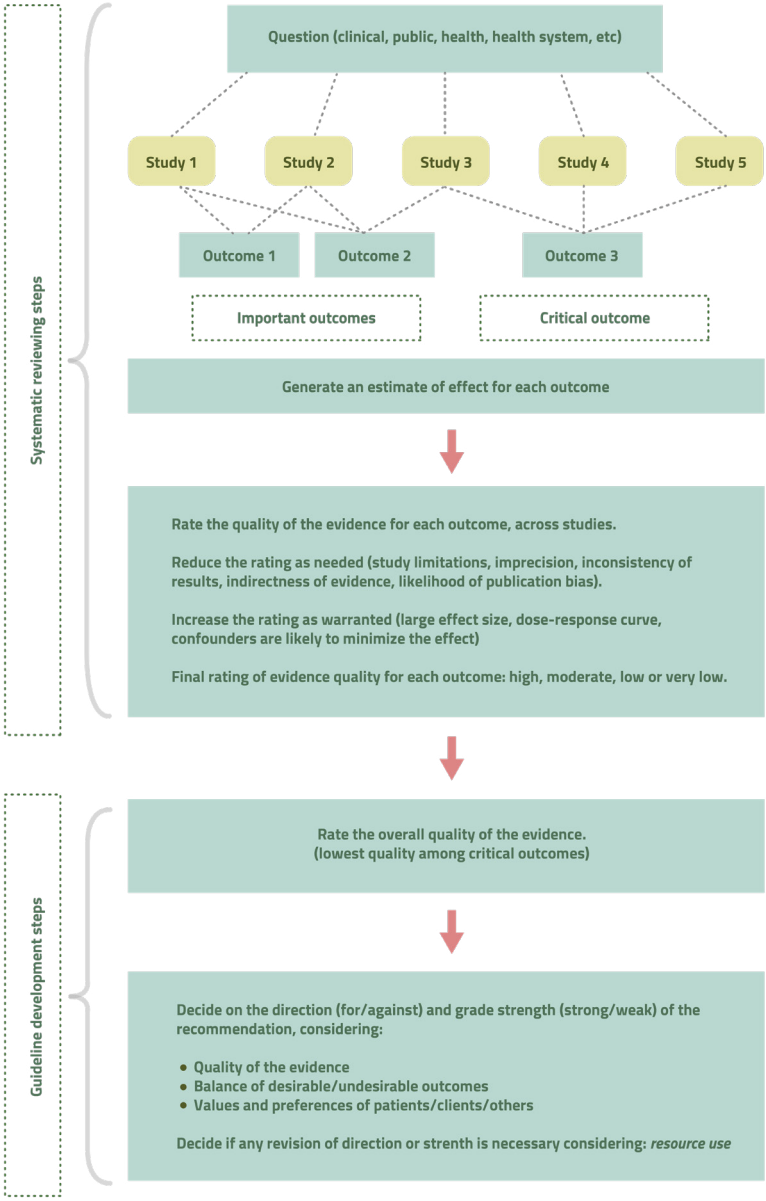
GRADE APPROACH

The appraised evidence that has been gathered in the SR needs to be assessed for quality. The GRADE approach has been recommended by WHO and is an international standard for assessing the quality of evidence and strength of recommendations of CPGs [Hsu J et al. 2011]. GRADE was developed by an international panel that considered clinical questions on diagnosis, screening, prevention, and therapy, making it applicable for use in a wide range of fields, including rehabilitation, public health, and health systems [Dijkers M 2013]. Detailed information is available on the GRADE website [http:// http://www.gradeworkinggroup.org/]. GRADE was initially published in a series of articles in the British Medical Journal in 2008, but since then, a more comprehensive discussion of the GRADE method can be found in a series of articles published in the Journal of Clinical Epidemiology from 2011 to 2017 [GRADE series JCE 2011-2017].

The GRADE methodology provides a systematic process of evaluating whether evidence may be downgraded or upgraded. Another advantage is that it requires the reviewer to explicitly state his judgment on the individual components that determines the quality of evidence for each outcome.

The steps of the GRADE method is summarized in Figure 4 [Guyatt G 2011].

FIGURE 4. OVERVIEW OF THE GRADE PROCESS.



Source: Guyatt G et al. GRADE guidelines:
1. Introduction - GRADE evidence profiles and summary of findings tables. JCE 64 (2011) 383e394

1. Rate outcomes

Outcomes are rated as important or critical by the Lead CPG Developers and CP, and a systematic search of relevant studies is undertaken to address the outcomes, as was previously described in Chapters 4 and 7.

2. Estimate of effect for each outcome

Reviewers use data from individual studies to generate the best estimate of effect of each patient-important outcome and an index (confidence interval [CI]) of the uncertainty associated with that estimate. The evidence for each patient-important outcome is summarized in an evidence profile or summary of findings table [Tables 7 and 8].

3. Rate quality of evidence for each outcome

The quality of evidence for each outcome is rated across studies. *A priori* ranking of "high" is assigned to randomized controlled trials and "low" to observational studies. Observational studies include interrupted time series (or quasi-experimental design), cohort studies and case-control studies, and other types of design such as case series and case reports. RCTs are given a higher grade because they are usually less prone to bias than observational studies.

The initial ranking of RCTs may be downgraded for the following reasons:

a. **Serious risk of bias due to study limitations** - These limitations include lack of clearly randomized allocation sequence, blinding, allocation concealment, or non-adherence to intention-to-treat analysis, or trial is cut short, or large losses to follow-up. Limitations for studies of diagnostic accuracy would exist if patients were not recruited consecutively but by disease condition and if both the diagnostic test and reference standard were done in all patients.

b. **Serious inconsistency between studies** - There is significant and unexplained variability in results from different trials as manifested by differences in the direction, size, and significance of the differences in effect.

c. **Serious indirectness** - There is an indirect comparison of two intervention or a mismatch on the population, outcome, or intervention between the CPG being developed and the existing available evidence.

d. **Serious imprecision** - There are wide CIs for the estimate of the effect, resulting from studies with few patients and events.

e. **Likely publication bias** - A systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies or selective reporting of outcomes.

Reasons for upgrading the ranking of observational studies are as follows:

- Large effect - the effect is so large and consistent that bias common to observational studies cannot possibly account for the result.
- Dose-response relationship - when the result is proportional to the degree of exposure, thus increasing the confidence in the findings
- Confounding variables - all possible confounders would only diminish the observed effect, and it is thus likely that the actual effect is larger than the data suggests

TABLE 5. QUALITY ASSESSMENT CRITERIA

STUDY DESIGN	QUALITY OF EVIDENCE	DOWNGRADE IN PRESENCE OF	UPGRADE IN PRESENCE OF
Randomized trial	High	**Risk of bias** (-1) Serious (-2) Very serious **Inconsistency** (-1) Serious (-2) Very serious **Indirectness** (-1) Serious (-2) Very serious **Imprecision** (-1) Serious (-2) Very serious **Publication bias** (-1) Serious (-2) Very serious	**Large effect** (+1) Large, no plausible confounders, consistent and direct evidence (+2) Very large, no major threats to validity and direct evidence **Dose response** (+1) Evidence of a gradient **All plausible confounding** (+1) Would reduce a demonstrated effect (+1) Would suggest a spurious effect when results show no effect
	Moderate		
Observational study	Low		
	Very low		

Source: Guyatt G et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. [Adapted Journal of Clinical Epidemiology 64 (2011) 383-394]

4. Rate quality of evidence for each outcome

The overall quality of the evidence is rated as “high”, “moderate”, “low”, or “very low” for all the critically important outcomes.

QUALITY OF EVIDENCE

TABLE 6. QUALITY OF EVIDENCE ACROSS OUTCOMES

QUALITY	DEFINITION	IMPLICATIONS
High	The group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Source: GRADE (modified)

EVIDENCE PROFILES

The results of an SR done for each PICO question are summarized in an evidence profile. This is in the form of a table that contains the quality assessment and summary of findings for each PICO question (Table 7).

TABLE 7. GRADE EVIDENCE PROFILE

QUALITY ASSESSMENT							NO OF PATIENTS		EFFECT		QUALITY*	IMPORTANCE
No of studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)	Absolute		
OUTCOME 1												
OUTCOME 2												

SUMMARY OF FINDINGS

The GRADEpro Guideline Development Tool (GDT) is used to create a Summary of Findings table (see Table 8), which presents the same information as an evidence profile after removal of the details of the quality assessment and after addition of comments. The table presents the number of patients or units studied, the quality of the evidence (4 levels), the magnitude of the effect (i.e., absolute and relative effects obtained from the SR), and the importance of the outcome (rating done during the scoping process). GRADEpro GDT can be accessed through https://gradepro.org/.

TABLE 8. SAMPLE OF A SUMMARY OF FINDINGS TABLE

PATIENT OR POPULATION:
SETTINGS:
INTERVENTION:
COMPARISON:

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk intervention	Corresponding risk comparison				

CI = confidence interval; GRADE = grading of recommendations, assessment, development , and evaluation

The succeeding steps in the GRADE process, "Rating the Overall Quality" and "Grading the Strength of the Recommendation", will be discussed in the next Chapter.

SUGGESTED READINGS

1. GRADE guidelines 17-part series 2011. Journal of Clinical Epidemiology.
2. GRADE equity guidelines 4-part series 2017. Journal of Clinical Epidemiology.
3. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html

CHAPTER TWELVE

ARRIVING AT CONSENSUS

After the evidence is synthesized (or in the case of adaptation of existing CPGs, evidence summaries are extracted), the evidence is then used to formulate the recommendations. The multi-sectoral CP undertakes the remaining steps in the GRADE process (Fig. 4).

1. **Rating the overall quality of the evidence**
   The CP receives and reviews all the information from the ERE to decide about which outcomes are critical and come to a final decision regarding the rating of the overall quality of evidence. The CP reviews the evidence summaries and draft recommendations to develop the final guideline recommendations. The direction and strength of the recommendation need to be considered. The recommendation could be in favor of one intervention or the other, but it is also possible that neither one of the alternative interventions could be recommended or that both interventions could be recommended as well.

2. **Grading the strength of recommendation**
   The CP meets to clarify and discuss the evidence summaries. The CP then votes on the final recommendation and the strength of the recommendation, based on the following primary considerations:

   a. **Quality of the evidence:** The evidence for each outcome reported is integrated into a summary of all outcomes. The evidence summary provides the basis for the strength of the recommendation for each clinical question. As the overall strength of evidence across outcomes increases, the recommendation would more likely be labeled as "strong." On the other hand, it would more likely to be labeled as "conditional" or "weak" as the overall strength of evidence decreases.

   b. **Balance between benefits and harms:** This is evaluated to determine if the net benefit outweighs the net harm. The balance between benefits and disadvantages (i.e., harm, burden, and cost) is assessed by weighing in the burden and the cost. Harm may be adverse reactions (i.e., burden in an unintended negative event accompanying the intervention) while costs pertain to the expense incurred during treatment and also for follow-up management. A greater difference between the desirable outcome (benefit) and the undesirable outcome (disadvantage) strengthens the recommendation for the intervention. The smaller the benefit is as compared to the magnitude of harm, then the likelihood of a conditional recommendation is greater, or a recommendation against the intervention is strengthened.

c. **Values, preferences, and burden on patients:** It is crucial that patients or patient advocates be adequately represented in the working groups of CPG development for the formulation of recommendations. Their opinions and experiences add to the certainty in values and preferences, thus making the recommendation stronger. A greater variability or uncertainty leads to a greater likelihood of a conditional recommendation.

d. **Cost and resource use:** This may be estimated by an economic evaluation. The more resource-intensive the intervention is, the lesser the likelihood that it will be strongly recommended. Uncertainty about resource use will most probably lead to a conditional recommendation. The CPG should explain how the implications of costs, resource use, and economic considerations were considered in determining the cost effectiveness of an intervention.

e. Other considerations that will increase the likelihood that an option or intervention will be strongly recommended include level of priority of the problem (i.e., greater burden of disease and baseline risk), equity and human rights (i.e., a greater reduction of inequity will result from implementing the intervention), and greater acceptability and feasibility of the option. There might be a need to make separate recommendations for subgroups for demographic issues regarding age, disability, gender, race, religion or beliefs, sex, sexual orientation, social issues like marriage and civil partnership, or clinical issues such as comorbidities or polypharmacy.

CONSENSUS METHODS

The voting process of the CP, utilizing formal methods, should be determined in advance in the CPG protocol. Initially, the nominal group technique is followed as the CP convenes in a face-to-face *en banc* meeting. Each member records his/her vote and presents it individually. All ideas are discussed. A consensus is reached when there is more than 75% agreement from the CP members both for the direction and strength of the recommendations. The voting is repeated at the most thrice until a consensus is reached.

When there are issues that are left unsettled after this meeting, the Delphi method is then employed by the CP as coordinated by the Lead CPG Developers. New evidence or adjusted perspectives may be presented in a questionnaire that is sent to the CP members via email and notified through a short message service (i.e., texting). Each member gets the chance to comment on the selected issues. The Lead CPG Developers synthesizes the comments. The comments and related feedback are anonymized and compiled and are then sent to the members for another round of voting. This may be done at most three times or until consensus is finally reached, whichever comes first. This method does not allow for the same live interaction among participants as the nominal technique but allows them to express their opinions more freely.

However, if a consensus regarding an issue is still not attained despite these efforts, the issue will be declared as undecided and will be stated as such in the final CPG manuscript.

CHAPTER THIRTEEN

PRODUCING THE GUIDELINES

WRITING RECOMMENDATIONS

The statement of recommendations consists of the quality of the evidence linked with the strength of the recommendation. All recommendations should be linked to the summary of evidence. If there is a mismatch between the strength of recommendation and the quality of evidence, justification on why it is for or against any intervention should be explicitly cited in the CPG. If a consensus cannot be reached about a recommendation, then it may be reported as "no definite recommendation can be made," but the process and discussion on the judgment should be explicitly stated in the guideline manuscript.

The recommendations in a guideline need to be clear, identifiable, and actionable. The language should be consistent and direct to avoid any ambiguity. The recommendation is written in an active voice and prescribes specific behavior required from the clinician to reduce variations in care (e.g., to improve diagnosis, to promote appropriate care, to avoid unnecessary tests or interventions, and/or to improve patient safety). Brief but precise supporting text should explain why the recommendation was made and how it is to be carried out. The recommendation describes who should do it, when or under what conditions it should be done, what is the action, and to whom it is directed [Rosenfeld RM, Shiffman RN, and Robertson P 2012].

WRITING THE MANUSCRIPT

It is ideal to employ only a single writer who will draft the CPG and is involved throughout the duration of the CPG development. The facilitating agency for guideline development contracted by the NCP secretariat along with the Lead CPG Developer assigns a scientific writer for each CPG being developed. Collation of all the evidence summaries and synthesis of the results of the CP meeting will be necessary. Documentation of the *en banc* CP meeting should be under the ERE responsibility. The final layout needs to be set before the manuscript is sent out for printing.

GUIDELINE FORMAT

In 2002, the Conference on Guideline Standardization (COGS) was convened to set the standards for guideline reporting that would promote guideline quality and facilitate implementation. The COGS checklist is a widely used tool for documentation of the guideline. It incorporates all the elements in the CPG protocol and provides a template for reporting of the recommendation statements. The checklist from the 2002 COGS [Shiffman RN et al. 2003] will be used for the standardized format of the completed CPG (Appendix E).

The CPG writer prepares different versions that will be used according to the target users: 1) a detailed full text, 2) a quick reference guide or abbreviated pocket guide, and 3) a brief, layman's version for the public.

IV. CPG APPRAISAL

CHAPTER FOURTEEN

EXTERNAL REVIEWS

APPRAISAL OF THE CPG

A methodological review of the completed CPG draft will be carried out by the QRP using the AGREE II instrument (Annex C).

The AGREE scores from each of the 5-member QRP will be pooled and analyzed. The acceptable cut off for the AGREE score will be set at an overall mean of 75%, with no domain scoring less than 75%. After at least 4 favorable recommendations of the 5 QRP members, the CPG will be submitted to the Secretary of Health for final approval as a DOH-endorsed CPGs or "National CPGs".

V. IMPLEMENTATION

CHAPTER FIFTEEN

DISSEMINATION

PUBLICATION

Dissemination plans should be part of the CPG protocol and should be strategized even before the CPG is completed. All DOH-endorsed or National CPGs shall be tagged with the quality appraisal result, rated using the AGREE II tool (whether they pass the minimum criteria or not). The DOH can partner with relevant stakeholders to undertake activities that will raise awareness of the new CPG. These activities may include, but are not limited to the following:

- Releasing a DOH memo to notify all stakeholders of the publication
- Publicizing the National CPGs through the DOH newsletter and alerts to appropriate agencies
- Issuing of a press release, releasing news articles, and utilizing social media accounts
- Creating tri-media advertisements (print, television, and radio)
- Organizing a press launch to allow information exchange between media and the guideline development groups
- Organizing a dissemination forum
- Conducting conferences, trainings, and implementation workshops
- Speaking engagements by experts in appropriate forums for the benefit of stakeholders and the general public
- Creating information, education, and communication materials for laymen and patients
- Developing a mobile app

CHAPTER SIXTEEN

MONITORING AND EVALUATION

The assessment of the effectiveness of the DOH-endorsed or National CPG would entail collection and synthesis of data reflecting its impact. A specific set of quality indicators should be formulated by the Lead CPG Developers in the CPG protocol to guide the DOH in monitoring and evaluation. Baseline data should be gathered prior to the release of the CPG and impact evaluation should be conducted 1-2 years after.

Evaluation systems can be built into the DOH framework to widen the responsibilities of existing standards and accreditation teams and to build their capacity to monitor outcome or performance measures related to CPG dissemination, adaptation, policy changes, changes in practice or policy, satisfaction of patients and practitioners, and other social or economic consequences.

UPDATING

Generally, it is advisable to revise a CPG every 3 years to coincide with the turnover of new evidence on the topic. A recent review of CPGs showed that as much as a fifth of recommendations contained in CPGs are considered outdated after 3 years [Garcia LM et al. 2014]. The Lead CPG Developers will designate a date by which it is expected that the validity of the CPG should be reviewed. Updates or revisions may be indicated if there are identified gaps in the current knowledge on the subject, newly released evidence from large scale studies, approval of new interventions or therapies, changes in critical or important outcomes, changes in values placed on outcomes, changes in resources available for health care, or potential need for new advice.

VI. REFERENCES

REFERENCES

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VII. APPENDICES

APPENDIX A.

CPG PROTOCOL FORMAT

I. SCOPE	
Title	State the title of the CPG. If it is a revised version, indicate as such in the title.
Topic	State the theme covered by the CPG. Description of the disease is warranted if the whole condition is to be covered. If only a certain aspect is to be tackled (e.g., diagnosis or therapy), describe the topic to be covered by combining words, such as "treatment of pediatric tuberculosis."
Background and context	State disease burden, describe background on intervention or topic.
Rationale	Explain why a CPG is needed.
Goal and objectives	State the CPG's general aim in terms of improving patient outcomes and specific objectives.
Expected target users and institutions	Describe the target audience or healthcare professionals expected to use the CPGs.
Related guidelines	If revised version, specify CPG that has been revised. If it is on a similar topic that has a published CPG, clarify the nature of this CPG and its relationship with the existing one.
Working groups	Enumerate members of Lead CPG Developers, Evidence Review Experts (ERE), and Consensus Panel (CP). Designate committee chairperson and vice chairperson, establish group processes and decision making. Indicate facilitating agency for guideline development if applicable.
Conflicts of interest	Describe collection, assessment, and management of Declarations of Conflicts of Interest (COIs).
Key clinical issues	State all key clinical issues to be covered in the CPG.
Range to be covered by CPG	Define in detail topics to be covered in the CPG. Describe separately the range to be covered and not to be covered by the CPG.
Key questions	List questions based on key clinical issues - both background and foreground (PICO) questions. List important and critical outcomes.

II. EVIDENCE REVIEW	
Need for new systematic review	Describe existing CPGs (if any) and determine if eligible for adaptation. If none, justify need for new SR to be undertaken.
Systematic review methods	Describe search strategy (including database selection and date range), study inclusion and exclusion criteria, evidence identification and retrieval, search process and yield, quality assessment of the primary studies, synthesis of the body of evidence for each outcome, and quality assessment of the body of evidence for each outcome. Describe the implementation schedule for the whole process.
III. EVIDENCE TO RECOMMENDATIONS	
Basic policy for formulating recommendations	Use of the GRADE approach, with incorporation of equity. Decide on the consensus method, factors to be considered for preparing recommendations, and the writing style.
Finalization of CPG	Describe procedures for finalizing the completed draft of the CPG.
Writing the CPG	Designate medical writer and editor.
IV. IMPLEMENTATION	
Dissemination	Describe the methods of dissemination, Describe the publication formats and derivative products. Describe methods of implementation and evaluation, including resource needs and quality indicators.
Updating	Describe plans for updating every 3 years.
V. LOGISTICS AND RESOURCES	
Funding	State process followed for allocation and approval of funding.
Budget	Specify in detail the components of the budget.
Timeline	Describe the timeline for the whole CPG development process.

APPENDIX B.

KNOWLEDGE MANAGEMENT PLUS (KM+) EQUITY CRITERIA

EQUITY LENS

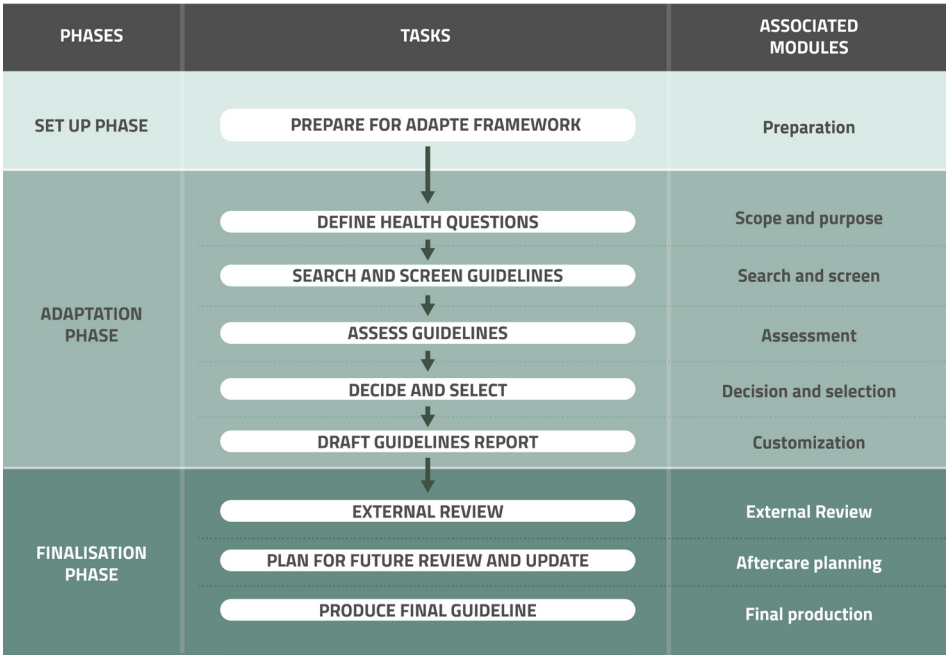
Criterion	Why it is important	What To Look For
Is the health problem a priority for all stakeholders, including potentially disadvantaged populations?	Disease priorities are often set by policy-makers, using criteria that they consider important. Patients are seldom asked what they consider important.	Look for patient involvement in the process, or at least, data showing the problem is important even for the socially disadvantaged.
Did the guidelines look into the possibility of differential effects of treatment (benefits and harms) in potentially disadvantaged populations*?	Differential effects may arise because of differences in patient compliance, physician compliance, health systems coverage, access and differential risk or psychosocial behaviors.	See if guideline developers sought data on effects of treatment in disadvantaged subgroups.
Is the voice/ interest of potentially disadvantaged populations represented in the expert panel?	Disadvantaged groups could be represented by practitioners who work with them, or by individuals from disadvantaged groups. Either could bring a unique perspective to the CPG development process.	See if disadvantaged subgroups or their caregivers are represented in the panel.
Is the voice/ interest of potentially disadvantaged populations represented in the feedback process?	Disadvantaged groups could be represented by practitioners who work with them, or by individuals from disadvantaged groups. Either could bring a unique perspective to CPG development.	See if disadvantaged subgroups or their caregivers are represented in the feedback process.

Criterion	Why it is important	What To Look For
Were feasible knowledge transfer strategies laid out to address barriers to the implementation of the guidelines in potentially disadvantaged populations*?	Knowledge transfer refers to strategies for dissemination and implementation of a particular guideline. What works on the average may not always work in disadvantaged populations.	Check for knowledge transfer strategies among disadvantaged population.
Does the impact assessment include evaluation of health gains across potentially disadvantaged populations*?	Measurement of the impact of an intervention is essential to track progress in reducing health disparities.	Check for plans on monitoring impact, paying special attention to disadvantaged populations.

Source: Acuin J, Dans A, Dans L, Dennis R, Deying K, Robinsin V. "Knowledge Plus" Program: Addressing Inequities in Clinical Practice Guidelines. Presentation made at Forum 9, Mumbai, India, 12-16 September 2005.

APPENDIX C.

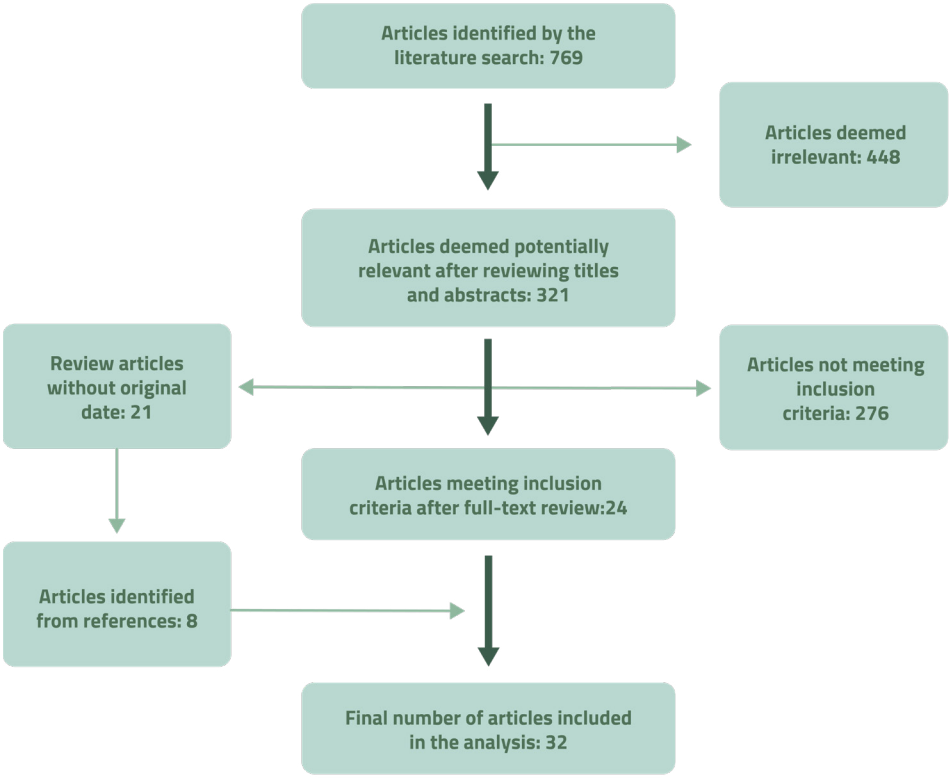
ADAPTE PROCESS



Source: ADAPTE Collaboration (2009). The ADAPTE Process: Resource Toolkit for guideline adaptation. Version 2.0 Available from: http://www.g-i-n.net.

APPENDIX D.

PRISMA FLOW DIAGRAM DEPICTING DISPOSITION OF ARTICLES



Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

APPENDIX E.

COGS CHECKLIST FOR REPORTING CLINICAL PRACTICE GUIDELINES

Topic	Description
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and electronic sources
2. Focus	Describe the primary disease/condition and intervention/service/ technology that the guideline addresses. Indicate any alternative preventive, 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. Users/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 interests 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 a 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 or harms

Topic	Description
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 thhis version of the guideline
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to minsinterpretation
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 strength, based on the criteria described in 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 references 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

Source: Shiffman RN et al. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med. 2003; 139:493-498.

VIII. ANNEXES

Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

JUL 02 2018

ADMINISTRATIVE ORDER
No. 2018 - 0019

SUBJECT: **Guidelines on the Institutionalization and Implementation of the National Clinical Practice Guidelines Program**

I. RATIONALE

Clinical practice guidelines (CPGs) are evidence-based recommendations used to optimize patient care by reducing inappropriate variations in practice and ensuring efficient use of limited resources. However, the lack of standardized process for developing and assuring quality of CPGs has resulted to their limited availability and large variations in quality.

In line with the Department of Health's (DOH) mandate as the lead agency in ensuring quality of health care through policy formulation, standards development and regulations as stated in Executive Order No. 102 s. 1999, there is a need for the DOH to facilitate the development of high quality CPGs that will be used to guide clinical practice of healthcare providers and provide guidance in the development of public health programs, health facilities and health workers standards, and benefit packages of the National Health Insurance Program.

II. OBJECTIVE

This Order aims to provide a framework for the continuous development of quality-assured CPGs. Specifically, this Order aims to institutionalize a standardized process for prioritization, generation, appraisal, dissemination, and implementation of CPGs through the establishment of a National Clinical Practice Guidelines Program (NCPGP).

III. SCOPE AND COVERAGE

This Order shall apply to all DOH Central Office Bureaus and Services, DOH Regional Offices, DOH Hospitals and Treatment Rehabilitation Centers, DOH attached agencies, and all other public and private entities involved in CPG development including but not limited to health care providers, academe, researchers and research institution and professional societies.

IV. DEFINITION OF TERMS

A. **Clinical Practice Guidelines (CPGs)** - recommendations intended to optimize patient care, which are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. (IOM, 2011)

B. **Conflict of Interest** - set of situations that creates a risk that professional judgment or actions regarding a primary interest shall be unduly influenced by a secondary interest. (IOM, 2011)

C. **Health Technology Assessment (HTA)** - the systematic evaluation of properties, effects, and/or impacts of health technology to inform policy decision making. (AO 2016-0034)

D. **Manual for CPG development** - pertains to the handbook containing the standards and prescribed methods set by the Department of Health on developing CPGs.

V. GENERAL GUIDELINES

A. The NCPGP shall standardize CPG development in the Philippines, encompassing the following processes in the CPG development: (1) Prioritization, (2) Generation, (3) Appraisal and Approval, and (4) Implementation and Dissemination (Annex A).

B. The NCPGP shall publish a Manual for CPG Development to inform the technical process of creating CPGs. The Manual shall outline specific methods for adapting existing guidelines, synthesizing and appraising evidence, developing recommendations, and writing the guideline manuscript.

C. Only CPGs that have met the quality standards as appraised by the National Guideline Clearinghouse and approved by the Secretary of Health (SOH) shall be recognized as DOH-endorsed CPGs or "National Guidelines."

D. DOH-endorsed CPGs or "National Guidelines" shall be used by healthcare providers, academe, and payers of healthcare to guide clinical practice and policy development.

E. The NCPGP shall develop and implement a monitoring and evaluation framework.

F. The CPGs shall be disseminated to relevant stakeholders through various effective channels identified by the DOH.

VI. SPECIFIC GUIDELINES

A. NCPGP Governance Structure

1. **National Guideline Clearinghouse (NGC)** shall appraise CPG manuscripts submitted by the CPG developers and endorse CPGs to the Secretary of Health for approval. The NGC shall be assembled by the NCPGP secretariat for each CPG that requires appraisal. The NGC shall be composed of the following: one (1) DOH representative, two (2) content experts, and two (2) methodologists.

2. **NCPGP Secretariat** shall manage and ensure effective implementation of the program.

3. **Lead CPG Developer**, the main point person or group who will spearhead the development of a CPG for a particular topic which may be a DOH Program Manager, a content expert and/or a methodologist, shall convene working groups to support CPG development. The working groups to be formed are as follows:

    a. A **Consensus Panel** composed of 10-15 multi-sectoral representatives from health care practitioners (specialists, generalists, primary care providers), patients and/or patient advocates, methodologists and other DOH representatives whose practice may be affected by the guideline or who can influence the uptake of CPG recommendations.

b. **Evidence Review Experts (ERE)** with at least one CPG/GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodologist, clinical epidemiologist or evidence-based practitioner and biostatistician. EREs shall conduct the review of existing CPGs, creating evidence summaries and formulating evidence-based draft recommendations.

B. **The National Clinical Practice Guideline Development Process**

1. **Prioritization.** DOH programs, health care providers, professional societies, and other relevant stakeholders may nominate topics to be considered for prioritization. The NCPGP secretariat shall facilitate a topic selection workshop to determine priority conditions that merit DOH funding for CPG development that shall be funded by the DOH based on a defined set of criteria (Annex B).

2. **CPG Generation.** CPG Developers shall convene working groups that are free from conflicts of interest. CPGs should be developed in accordance to the prescribed methods in the Manual for CPG Development. Completed CPG manuscripts shall be submitted to the NGC for appraisal.

3. **Appraisal and Approval.** The NGC shall use GRADE approach in appraising CPG manuscripts. CPGs that pass the quality assessment shall be endorsed to the SOH for approval and adoption, while those that do not pass the review shall be turned over to the CPG developer for improvement.

4. **Dissemination and Implementation.** The NGC shall ensure that there is a dissemination plan for DOH-endorsed CPGs or "National Guidelines". A full text, pocket guide, and laymanized versions of the CPG shall also be produced by the CPG developers. The NCPGP secretariat shall keep a library or repository of DOH-endorsed CPGs.

C. **Management of Conflicts of Interest**

1. Declaration and management of conflicts of interest shall be mandatory for all groups and persons involved in the NCPGP. All stakeholders involved in the CPG development process shall comply with existing DOH guidelines on the management of conflict of interest (COI).

2. All CPGs submitted by CPG developers shall undergo an assessment of COI. CPGs that violate the COI policy shall be recommended for disapproval and shall not be endorsed by the DOH.

D. **Integration with the Health Technology Assessment Program**

1. The NCPGP shall collaborate with the Health Technology Assessment (HTA) program to ensure consistency in the outputs, evidence used, and recommendations.

2. The NCPGP may inform or be informed by the evidence generated through the HTA Program.

VII. ROLES AND RESPONSIBILITIES

A. The **Health Policy Development and Planning Bureau (HPDPB)** shall act as the NCPGP secretariat who shall provide technical and administrative support to the NCPGP such as but not limited to the following: (1) facilitation of the topic prioritization process for DOH-funded CPG development (2) provision of technical support during NGC meetings, and (3) ensure monitoring and evaluation of the NCPGP.

B. The **Health Facility Development Bureau (HFDB), Disease Prevention and Control Bureau (DPCB) and the Philippine Health Insurance Corporation** shall (1) provide appropriate financial and technical support in the development of National CPGs, (2) utilize National CPGs in the design of DOH programs and PHIC policies, and (3) aid in the dissemination, implementation, monitoring, and evaluation of National CPGs.

VIII. REPEALING CLAUSE

All issuances inconsistent with the provisions of this Order are hereby revised, modified or rescinded accordingly. All other provisions of existing issuances which are not affected by this order shall remain valid and in effect.

IX. SEPARABILITY CLAUSE

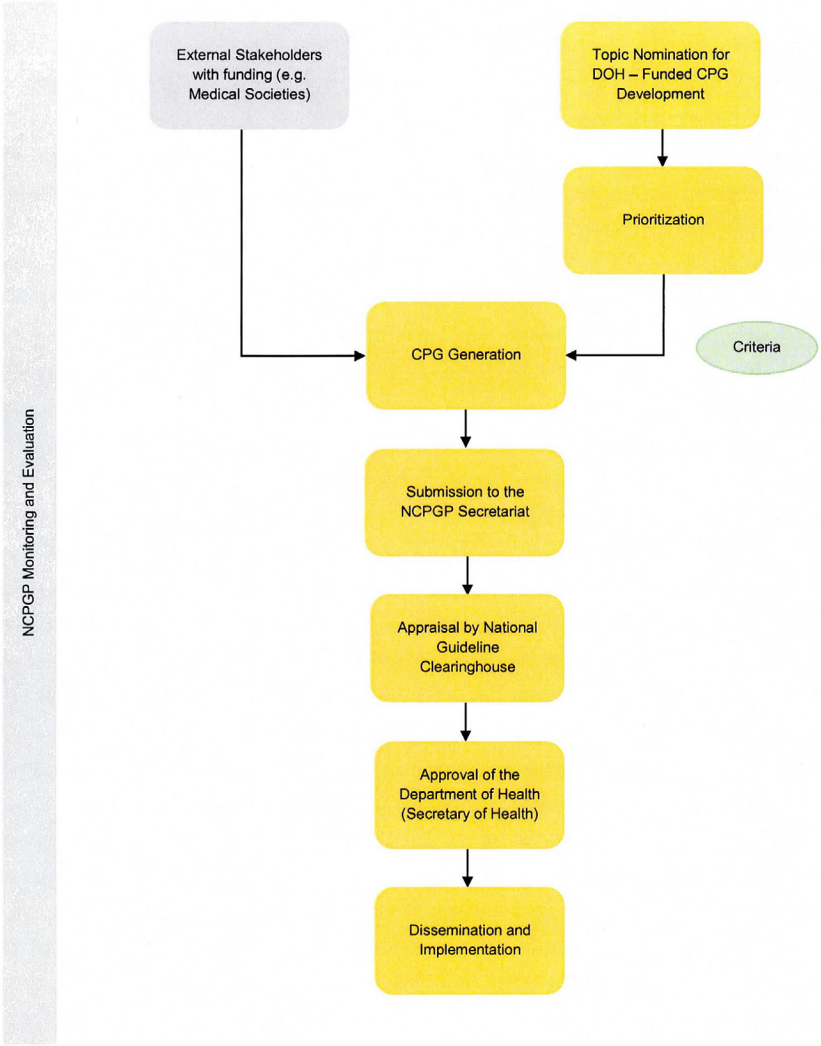
If any provision of this Order is declared invalid, unenforceable or unconstitutional, the validity or enforceability of the remaining provisions shall not be affected, and this Order shall be interpreted as if it did not contain the particular invalid, enforceable or unconstitutional provision

X. EFFECTIVITY

This Order shall take effect immediately.

FRANCISCO T. DUQUE III, MD, MSc
Secretary of Health

Annex A. Clinical Practice Guidelines Development Process



Annex B. Prioritization Criteria

Criteria	Definition
1. Disease Burden	The prevalence, co-morbidity, mortality, quality of life and effectiveness of the preventive service on patients, their families, and communities
2. Public Contention	Public interest surrounding the topic or disease condition
3. Cost-effectiveness	Economic evaluation
4. New evidence	Recent evidence that can potentially change previous recommendations
5. Potential impact	Potential to improve health outcomes and quality of life, or in decision-making resulting in practice change
6. Interest of public or care providers	Recommendations by practitioners or stakeholders
7. Variation in care	Potential to decrease variation in care (i.e. prevention, diagnosis or treatment)
8. Sufficiency of evidence	Availability of clearly defined and high quality evidence
9. Timeliness	Urgency for guideline to be developed

ANNEX B.

DECLARATION OF CONFLICT OF INTERESTS FORM

PERSONAL INFORMATION	
CPG Title:	
Name:	
Designation:	
Institution:	
Mobile no:	
Email address:	
CPG Group:	
Function/Role:	

POLICY ON COI

1. You have been invited to participate in this CPG development project because of your professional standing and expertise.
2. You must disclose any circumstance that could represent a potential conflict of interest.
3. You must disclose on this Declaration of Conflict of Interest Form any financial, professional, or other interest relevant to the subject of the CPG in which you have been asked to participate in or contribute towards, and any interest that could affect the outcome of the project. You must also declare relevant interests of your immediate family members and, if you are aware of it, relevant interests of other parties with whom you have substantial common interests and which may be perceived as unduly influencing your judgment.
4. This declaration form must be completed before participation in the CPG project activity can be confirmed.
5. Answering "Yes" to a question on this form does not automatically disqualify you or limit your participation in the CPG project. Your answers will be reviewed by the facilitating agency or Contracted Research Agency (CRA) to determine whether you have a COI relevant to the subject of the CPG, and the COI will be managed accordingly.
6. You must promptly inform the CRA if there is any change in this information prior to or during the course of your work on the CPG project.
7. Incomplete disclosure of all relevant information on this form may, depending on the circumstances, lead the CRA to decide not to appoint you to future CPG development projects.

8. This declaration applies only to current conflicts of interest (not more than 4 years). It does not apply to past interests that have expired, no longer exist, and cannot reasonably affect current behavior.

CONFLICTS OF INTEREST STATEMENT

Please answer each of the questions below. If the answer to any of the questions is "yes", briefly describe the circumstances. The term "you" refers to yourself and your immediate family members. **If you do not describe the nature of an interest or if you do not provide the amount or value involved where relevant, the conflict will be assumed to be significant.**

Items	Yes	No	Type	Name of company, organization or institution	Declarer (you), spouse / partner or research unit	Amount of income or value of interest	Period
1. **Employment and Consulting:** Within the past 4 years, have you received renumeration from a commercial entity or other organization with an interest related to the subject of the CPG?							
a. Employment							
b. Consulting (as technical or other advisor)							
2. **Research Support:** Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the CPG?							
a. Research support, including grants, collaborations, sponsorships, and other funding							
b. Non-financial support valued at more than PhP 50,000 overall - equipment, facilities, research assistants, paid travel to meetings, etc.)							

Items	Yes	No	Type	Name of company, organi-zation or institution	Declarer (you), spouse / partner or research unit	Amount of income or value of interest	Period
c. Support (including honoraria) for being on a speakers' bureau, and/or giving speeches or training for a commercial entity or other organization with an interest related to the subject of the CPG							
3**. Investment Interests:** Do you have investments in any commercial entity with an interest related to the subject of the CPG? (Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds, or similar investments that are broadly diversified and over which you exercise no control.)							
a. Stocks, bonds, stock options, other securities (e.g., short sales)							
b. Commercial business interests (proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)							

Items	Yes	No	Type	Name of company, organi-zation or institution	Declarer (you), spouse / partner or research unit	Amount of income or value of interest	Period
4. **Intellectual Property:** Do you have any intellectual property rights that might be enhanced or diminished by the outcome of the CPG?							
a.Patents, trademarks, or copyrights (including pending applications)							
b.Proprietary know-how in a substance, technology, or process							
5. Non-financial interests: Are you engaged in any professional or other activities which outside parties could consider might represent or give rise to a conflict of interest, or the perception of a conflict of interest with regard to your CPG work							
	Yes	**No**	**Type**	**Designation**	**Name of company, organization or institution, or journal**		**Details**
a. Author/ co-author of a published paper related to the CPG topic							
b.Senior editorial role or assignment							
c. Official function in a government agency or international organization							

	Yes	No	Type	Designation	Name of company, organization or institution, or journal		Details
d. Advisory committee associated with a public or private sector organization							
e. Board member of a public or private sector organization							
f. Board member of a non-profit organization							
g. Board member of an advocacy group							
6. Public Statements and Positions (during the past 4 years)							
	Yes	**No**	**Subject**	**Circum-stances**	**Parties Involved**	**Time Frame**	**Other Details**
a. Have you given expert testimony (with regard to any regulatory, legislative or judicial process) related to the subject of the CPG, for a commercial entity or other organization?							

	Yes	No	Subject	Circum-stances	Parties Involved	Time Frame	Other Details
b. Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the CPG?							
7. Additional Information							
	Yes	No	Subject	Circum-stances	Parties Involved	Time Frame	Other Details
a. If not already disclosed above, have you worked for the competitor of a product that is the subject of the CPG, or will your participation in this project or work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial, or business competitive advantage?							

	Yes	No	Subject	Circum-stances	Parties Involved	Time Frame	Other Details
b. To your knowledge, would the outcome of this CPG project or work benefit or adversely affect interests of others with whom you have substantial common personal, professional, financial, or business interests (such as your adult children or siblings, close professional colleagues, administrative unit or department)?							
c. Excluding this CPG project, has any person or entity paid or contributed towards your travel costs in connection with this work?							
d. Have you received any payments (other than for travel costs) or honoraria for speaking publicly on the subject of this CPG or work?							

	Yes	No	Subject	Circum-stances	Parties Involved	Time Frame	Other Details
e. Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?							

	YES	NO
7. Tobacco or Tobacco Products (answer without regard to relevance to the subject of the meeting or work): Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?		

CONSENT TO DISCLOSURE.

By completing and signing this form, you consent to the disclosure of any relevant conflicts to other CPG group members and in the final CPG manuscript.

DECLARATION.

I hereby, declare on my honor, that the disclosed information is true and complete to the best of my knowledge and belief.

Should there be any change to the above information, I will promptly notify the responsible staff of the facilitating agency for CPG development or CRA and complete a new declaration of conflict of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final CPG manuscript or completion of the activity concerned.

DATE

SIGNATURE

ANNEX C.

AGREE II INSTRUMENT

1	2	3	4	5	6	7
Strongly disagree						Strongly agree
DOMAIN 1. SCOPE AND PURPOSE						
1. The overall objective(s) of the guideline is (are) specifically described.						
2. The health question(s) covered by the guideline is (are) specifically described.						
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.						
DOMAIN 2. STAKEHOLDER INVOLVEMENT						
4. The guideline 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 guideline are clearly defined.						
DOMAIN 3. 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 guideline has been externally reviewed by experts prior to its publication.						
14. A procedure for updating the guideline is provided.						
DOMAIN 4. 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.						

DOMAIN 5. APPLICABILITY	
18. The guideline describes facilitators and barriers to its application.	
19. The guideline 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 guideline presents monitoring and/or auditing criteria.	
DOMAIN 6. EDITORIAL INDEPENDENCE	
22. The views of the funding body have not influenced the content of the guideline.	
23. Competing interests of guideline development group members have been recorded and addressed.	
OVERALL GUIDELINE ASSESSMENT	
1. Rate the overall quality of this guideline	
2. I would recommend this guideline for use	
Yes	
Yes, with modifications	
No	
NOTES:	

Source: Browers M et al. For the AGREE Next Steps Consortium. 2010

ANNEX D.

GUIDE QUESTIONS FOR APPRAISING A SYSTEMATIC REVIEW

I. APPRAISING DIRECTNESS
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/ intervention (E) and outcome (O)?
II. APPRAISING VALIDITY
1. Were the criteria for inclusion of studies appropriate?
2. Was the search for eligible studies thorough?
3. Was the validity of the included studies assessed?
4. Were the assessments of the studies reproducible?
III. APPRAISING RESULTS
1. What are the overall results of the review?
2. Were the results similar from study to study?
3. How precise were the results?
IV. ASSESSING APPLICABILITY
1. Are there biologic issues affecting applicability? (Consider the influence of sex, co-morbidity, race, age and pathology)
2. Are there socio-economic issues affecting applicability?
3. If the overall results of the review are not directly applicable to your patient, are there credible subgroup analyses that you could use?
V. INDIVIDUALIZING THE RESULTS
1. What is the implication of study findings on your individual patient? (Estimate the individualized NNTs for your patient)
2. Would you offer the treatment to your patients?

Source: Chapter 6. Painless Evidence-Based Medicine. 2nd ed

ANNEX E.

GUIDE QUESTIONS FOR APPRAISING AN ARTICLE ON THERAPY

I. APPRAISING DIRECTNESS
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/ intervention (E) and outcome (O)?
II. APPRAISING VALIDITY
1. Were patients randomly assigned to treatment groups?
2. Was allocation concealed?
3. Were baseline characteristics similar at the start of the trial?
4. Were patients blinded to treatment assignment?
5. Were caregivers blinded to treatment assignment?
6. Were outcome assessors blinded to treatment assignment?
7. Were all patients analyzed in the groups to which they were originally randomized?
8. Was follow-up rate adequate?
III. APPRAISING RESULTS
1. How large was the effect of treatment?
2. How precise was the estimate of the treatment effect?
IV. ASSESSING APPLICABILITY
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)
2, Are there socio-economic issues affecting applicability of treatment?
V. INDIVIDUALIZING THE RESULTS
1. What is the likely effect of the treatment on your individual patient? (Estimate the individualized NNT* for your patient)
2. Would you offer the treatment to your patients?

Source: Chapter 2. Painless Evidence-Based Medicine. 2nd ed.

**NNT – number needed to treat*

ANNEX F.

GUIDE QUESTIONS FOR APPRAISING AN ARTICLE ON DIAGNOSIS

I. APPRAISING DIRECTNESS
Does the study provide a direct enough answer to your clinical question in terms of patients (P), examination (E) used and disease or outcome (O) being diagnosed?
II. APPRAISING VALIDITY
1. Was the reference standard an acceptable one?
2. Was the reference standard interpreted independently from the test in question?
III. APPRAISING RESULTS
What likelihood ratios were associated with the range of possible test results?
IV. ASSESSING APPLICABILITY
1. Are there biologic issues that may affect accuracy of the test? (Consider the influence of sex, co-morbidity, race, age and pathology)
2. Are there socio-economic issues that may affect accuracy of the test?
V. INDIVIDUALIZING THE RESULTS
1. How will the test results affect the probability of disease in your patient? (Estimate the individualized post-test probability of your patient)
2. Is this test useful for your patient?

Source: Chapter 2. Painless Evidence-Based Medicine. 2nd ed.

ANNEX G.

GUIDE QUESTIONS FOR APPRAISING AN ARTICLE ON HARM

I. APPRAISING DIRECTNESS
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/ intervention (E) and outcome O)?
II. APPRAISING VALIDITY
1. Did exposure precede outcome in the study?
2. Were the patient groups being compared sufficiently similar with respect to baseline characteristics? If not, were statistical adjustments made?
3. Were unbiased criteria used to determine exposure in all patients?
4. Were unbiased criteria used to detect outcome in all patients?
5. Was follow-up rate adequate?
III. APPRAISING RESULTS
1. How strong is the association between exposure and outcome?
2. How precise is the estimate of the risk?
IV. ASSESSING APPLICABILITY
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)
2. Are there socio-economic issues affecting applicability of treatment?
V. INDIVIDUALIZING THE RESULTS
1. What is the likely effect of the exposure on the risk of your individual patient? (Estimate the individualized NNT/NNH* for your patient)
2. Would you ask the patient to avoid the exposure?

Source: Chapter 2. Painless Evidence-Based Medicine. 2nd ed.

** NNT/NNH – number needed to treat/number needed to harm*

ANNEX H.

GUIDE QUESTIONS FOR APPRAISING AN ARTICLE ON PROGNOSIS

I. APPRAISING DIRECTNESS
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/ intervention (E) and outcome O)?
II. APPRAISING VALIDITY
1. Was the sample of patients' representative?
2. Were patients (or subgroups of patients) sufficiently homogeneous with respect to prognostic factors?
3. Were objective & unbiased outcome criteria used?
4. Was follow-up rate adequate?
III. APPRAISING RESULTS
1. How likely are the outcomes over time?
2. How precise are the estimates of likelihood?
IV. ASSESSING APPLICABILITY
1. Are there biologic issues that may affect applicability? (Consider the influence of sex, co-morbidity, race, age and pathology)
2. Are there socio-economic issues affecting applicability?
V. INDIVIDUALIZING THE RESULTS
What is the estimate of prognosis in your patient?

Source: Chapter 2. Painless Evidence-Based Medicine. 2nd ed.