ROLES OF CLINICAL PRACTICE GUIDELINES OUTSIDE THE CLINICAL ENCOUNTER

ROLES OF CLINICAL PRACTICE GUIDELINES OUTSIDE THE CLINICAL ENCOUNTER

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Abstract

Clinical practice guidelines (CPGs) are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. CPGs' recommendations have traditionally focused on informing clinicians and patients on the best options, i.e., supporting decisions that occur at the clinical encounter level. Considering all their advantages (a systematic and comprehensive review of the evidence, a multidisciplinary team assessing the evidence and balancing benefits and harms, and the additional considerations such as patients' preferences, implementability and feasibility of interventions and their costs) CPGs have also become powerful tools to inform decisions and activities outside the clinical encounter. This, because the clinical encounter cannot be completely separated from other decisions that indirectly affect that level, such as those related to quality improvement activities and economic decisions in healthcare. Moreover, activities that are not directly related to the clinical encounter can benefit from CPGs, like education and licensing activities and research prioritization processes, or judicial decisions. The role of CPGs in all these activities has been neglected in the literature.

In this study, I performed a critical interpretive synthesis of the literature to summarize the different roles CPGs play outside the clinical encounter and to understand how, and under what conditions CPGs are used in these roles. I also conducted an international survey to describe how frequent these roles exist, from the CPGs developers' perspectives. Lastly, I conducted a multiple case study to understand how and under what conditions CPGs play one of the main roles outside the clinical encounter (drug funding decisions), in two different settings (Colombia and Canada/Ontario).

Based on the results, I developed a framework to describe and categorize the roles of CPGs outside the clinical encounter and to determine how and under what conditions CPGs are used in these roles. I highlighted the key areas that require additional methodological research and categorize the roles in main, secondary and unanticipated roles. I also described how international developers reported that CPGs play

these roles and how these roles are part of their CPGs final aims in the second study. Lastly, in the case study, I revealed that CPGs were instrumentally used to inform one of the main roles, drug funding decisions, in the Colombian case, and they had a minor conceptual use in the case of Canada/Ontario.

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List of Abbreviations

AGREE II:	Appraisal of Guidelines for Research & Evaluation II (Tool)
AGREE-REX:	Appraisal of Guidelines for Research & Evaluation Recommendations Excellence (tool)
AHRQ:	Agency for Healthcare Research and Quality
BIA:	Budget impact analysis
CADTH:	Canadian Agency for Drugs and Technologies in Health
CINAHL:	Cumulative Index to Nursing and Allied Health Literature
CCO	Cancer Care Ontario
CEA:	Cost-effectiveness analysis
CGR	Clinical Guidance Report
CIS:	Critical Interpretive Synthesis
CME:	Continuing Medical Education
CPG:	Clinical Practice Guideline
DM:	Decision makers group
EBM:	Evidence-Based medicine
EGR	Economic Guidance Report
GAI:	*Guías de Atención Integral* (Comprehensive Care Guidelines)
G-I-N:	Guidelines International Network
GINAHTA:	G-I-N and INAHTA (International Network for Technology assessment) working group
GOBSAT:	Good Old Boys Sat Around a Table
GRADE:	Grading of Recommendations, Assessment, Development and Evaluations
HiREB:	Hamilton Integrated Research Ethics Board
HSG	Health Systems Guidance
HTA:	Health Technology Assessment
IETS:	*Instituto de Evaluación Tecnológica en Salud* (Colombian HTA agency)

IOM:	Institute of Medicine
IQR:	Interquartile range
KT:	Knowledge translation
LILACS:	Latin American and Caribbean System on Health Sciences Information (database)
MOC:	Maintenance of Certification
MG	Methodological guideline
MoH:	Ministry of Health
NICE:	National Institute for Health and Care Excellence
NIHR:	National Institute of Health Research
P4P:	Pay for performance
pCODR	pan-Canadian Oncology Drug Review
PEBC	Program in Evidence-Based Care
pERC:	pCODR Expert Review Committee
PICO:	Population, Intervention, Comparison and Outcome(s) framework
POS:	*Plan Obligatorio de Salud* (Colombian Mandatory Health Plan)
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PR:	"Prioritizers" group
PROSPERO:	International prospective register of systematic reviews (Database)
QI:	Quality indicators
RCTs:	Randomized Controlled trials
SPOR:	Strategy for Patient-Oriented Research Alliance
SY:	Synthesis group
UK:	United Kingdom
US:	United States

Preface

This dissertation has been conducted as a "sandwich thesis" and includes three individual manuscripts that will be submitted for peer review and publication in scientific journals. These are:

1. **Chapter 1:** Introduction to the thesis
2. **Chapter 2:** Identifying the roles of clinical practical guidelines in health care decision-making beyond the clinical encounter: a critical interpretive synthesis
3. **Chapter 3**: Roles of the clinical practice guidelines outside the clinical encounter: An International Survey of Guidelines Developers
4. **Chapter 4**: Clinical practice guidelines' role in drug funding decisions in Ontario (Canada) and Colombia: a multiple case study
5. **Chapter 5**: Conclusion

Table 1 below, summarizes each study, their key characteristics, designs and contributions

Table 1. Detailed description of the studies characteristics, designs and contributions

	Study 1 (Chapter 2)	**Study 2 (Chapter 3)**	**Study 3 (Chapter 4)**
Title of the study	Identifying the roles of clinical practical guidelines in health care decision-making beyond the clinical encounter: a critical interpretive synthesis	Roles of the Clinical Practice Guidelines' Recommendations outside the clinical encounter: An International Survey of Guidelines Developers	Clinical practice guidelines' role in drug funding decisions in Ontario (Canada) and Colombia: a multiple case study
Questions addressed	• What roles CPGs play in decision-making outside the clinical encounter? • How CPGs play these roles? • Under what conditions are they used in these roles?	• What are the roles reported by international guidelines developers of their CPGS outside the clinical encounter? • How frequent developers, consider that their CPGs recommendations are used for these roles? • How frequent developers consider stakeholders in charge of those activities as target users of their CPGs	• Have CPGs played a role in drug funding decisions? • How are CPGs used in drug funding decisions? • Under what conditions CPGs have been used for this role?
Design	Critical interpretive synthesis	Cross sectional study	Multiple case study

Data source	Scholarly literature	International survey of CPGs' developers	Interviews and document analyses focused on the views and experiences of CPGs developers, HTA agencies and decision-makers
Connection between the studies	A framework was developed; it was later used to design the study 2	Survey was designed based on the results of the framework developed in study 1	One of the main roles pointed out in study 1 (economic/coverage decisions), which was also found reported by almost half of developers in study 2, was chosen to focus the analysis in study 3. The aim was to understand whether the selected roles was present and how, an under what conditions CPGs were used in that role
Substantial contribution	Provides two new theoretical frameworks. First, we described and explain what the roles of CPGs outside the clinical encounter are. Second, our framework explains how CPGs play these roles, what methodological tools exist to facilitate this role and what areas require further development	Describes the current status of the presence of each one of the roles (main, secondary and unanticipated role), from the perspective of international developers.	Provides the first analysis to understand whether CPGs play roles in supporting dug funding decisions in Canada/Ontario and Colombia, and how and under what conditions CPGS were used in these roles
Theoretical contribution	Identifies three major categories of roles of CPGs outside the clinical encounter: main roles, secondary roles and unanticipated role. Under these three categories a total of 15 roles were described	Describes the frequency the roles found in study 1 were reported by some of the most important international guideline developers	Provides explanations of how and under what conditions CPGs have been used in two different jurisdictions (Colombia and Canada/Ontario)
Methodological contribution	The theoretical framework synthesizes the available sparse and diverse evidence of a study field that has been neglected. Also, the framework of "how the CPGs play the roles", highlight key methodological gaps in the literature that needs to be addressed to facilitate the roles of CPGs.	The survey highlighted how all developers explicitly reported one or more roles of CPGS outside the clinical encounter and how stakeholders in charge of these roles are their target users. This highlights key methodological work that needs to be addressed, to determine if CPGs may need to be modified to fit into these roles. Also, our survey illustrated the utility of the framework developed in study 1	This case study has highlighted key methodological considerations that will be helpful for developers in cases where CPGs are to be considered for informing drug funding decisions. For instance, the relationship between HTA and CPG in different contexts requires further study. It is not clear what might be the best model of collaboration between both evidence-based documents. Methodological work to fill this gap is needed.

Declaration of academic achievement

This dissertation presents three original scientific contributions (chapters 2-4), along with introductory and concluding chapters (chapters 1 and 5). Each of the chapters in this dissertation is co-authored, and I, Ivan Florez, am the lead author for each. Overall, I conceived each study with my supervisor, Dr. Melissa Brouwers, and with substantial input from members of my supervisory committee, Dr. John Lavis and Dr. Holger Schünemann. Additionally, Chapter 2 had additional input from Dr Marcela Velez who participated in the article's selection process and analysis. Chapter 3, as well, had some input form Dr Yasser Samir Amer and Robin Vernooij who provided feedback and comments to the protocol and participated in the data collection process.

I am responsible and made the following contributions in all projects included in this dissertation: design, conception, analysis, and writing of manuscripts. I designed the search strategy, screening, and data extraction, and analyses of the critical interpretive synthesis (Chapter 2); I designed the survey and lead the data collection process of the cross sectional study, and designed and conducted the analysis (Chapter 3); I designed the interview scripts, and I conducted all the interviews, transcriptions and analyses for the case study (chapter 4). Finally, I drafted all chapters, and each co-author provided feedback that was incorporated into subsequent revisions. Each article will be submitted to specific scientific journals.

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CHAPTER 1: INTRODUCTION

Chapter 1: Introduction

This chapter introduces a Ph.D. dissertation that consists of three original research chapters (Chapters 2 to 4). This introduction presents an overview of the roles of clinical practice guidelines (CPGs) in decisions and activities outside the clinical encounter.

Evidence-based Clinical Practice Guidelines

Some have argued that CPGs are as old as medical textbooks or even as old as the clinical training itself. However, CPGs that provide recommendations developed by organizations (professional societies or government bodies) to inform clinical practice have existed for approximately six to seven decades. Some of the alternative terms that have been used to describe them are: "practice standards," "recommendations," "protocols," "policies," "practice parameters," and "practice options" (1).

The first traceable CPGs were consensus statements, which, in the United States (US), were initially developed and funded by professional associations, and decades later, mostly in other countries, by governmental organizations. These CPGs provided recommendations that were agreed on during conferences (consensus conferences) and based on the participants' experience and opinions (2). Although initially considered appropriate to meet the goals of fostering clinician agreement and to reduce inappropriate variability among practitioners, this approach soon proved to be inadequate. This methodology has been called GOBSAT (Good Old Boys Sat Around a Table) and refers to the process by which self-selected experts discuss their (often subjective) opinions and provide recommendations. This approach has proved to be problematic for several reasons. The process is non-systematic, non-transparent, potentially biased towards the positions of influential (or domineering) persons, at risk of influence associated to undeclared conflicts of interests, and it fails to ensure relevant evidence is considered, and appraised (3, 4). Thus, currently, there is a general agreement that CPGs

recommendations derived solely from this approach do not provide sufficient grounds for appropriate clinical care (5).

Then, in the 1990s, the idea of evidence-based medicine (EBM) emerged from the academic environment. The EBM movement was born to train physicians to critically appraise the medical literature and use evidence to make better clinical decisions (6, 7). Although far from perfect, the initial EBM philosophy has facilitated the skills among physicians in creating clinically important questions, searching and retrieving the literature, critically appraising the evidence, and informing decisions. The EBM movement was crucial in de-emphasizing intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making (5). Gradually, CPGs started using the EBM approach to develop systematic reviews of the evidence to answer clinically relevant questions and provide evidence-based recommendations (7). This newer generation of CPGs, now evidence-based, started being the ideal methodological approach to develop more transparent recommendations.

As a result of this evolution, more recent definitions of CPGs include the requirement of a systematic review of the evidence and transparent and thoughtful consideration of the trade-offs between benefits and harms. These expectations are reflected in the definitions from the National Academy of Medicine (formerly, Institute of Medicine) that states that CPGs “are statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"(8).

Moreover, although not included in the definitions, additional factors have been more recently identified as key to inform the CPGs process. The consideration of patients’ values and preferences, costs and use of resources, and the feasibility and applicability of the recommended actions have been identified as critical in the recommendations process. The most used appraisal tools to assess the quality of CPGs (the Appraisal of Guidelines Research and Evaluation, the AGREE II tool, and more recently, the AGREE-REX tool), the most accepted CPG development methodological approach (the Grading of

Recommendations, Assessment, Development and Evaluations; GRADE approach) and the largest international guidelines organization (the Guidelines International Network, G-I-N) (9-11) all agree that these features are essential parts of CPGs development. The reason behind this expansion is the need to develop recommendations that are ideal from an evidence-based perspective, but also feasible, usable, and acceptable. Recommendations that are only based on the evidence and the balance between benefits and harms without considering the factors mentioned above are at risk of not being applied because interventions might not be available, might be too expensive or too challenging to put in practice in particular contexts, or patients will not accept them.

In summary, CPGs evolved from consensus-based statements to recommendations that use evidence-based methods to work with research evidence, and later to systematically consider patients' values and preferences, costs and resources use and feasibility of the recommendations. Namely, CPGs became a powerful tool that involved a comprehensive evidence search with other considerations to provide recommendations aiming to support clinical decisions in the best way possible.

The clinical encounter and other activities

The clinical encounter is defined by physical or virtual contact between a subject/patient and healthcare practitioner/researcher, during which an assessment or clinical activity is performed (12). CPGs have traditionally informed the decisions that are made at this level. In fact, recommendations are usually written with the aim of providing advice in specific clinical scenarios, and thus, the expected action from them are decisions on clinical management focused on the patient.

Although the clinical encounter is a scenario where practitioners and patients are the only direct actors, it is not possible to completely separate this encounter from other decisions. Activities outside the clinical encounter, such as those at the management or health system levels could directly or indirectly influence clinical decisions. The health care system and the setting can impede or facilitate opportunities

for the clinical decision to be put in practice (1, 13, 14). Therefore, recommendations focused on informing the clinical encounter end up being of interest to other actors in the health system and other fields.

For example, activities related to the quality of care priorities or decisions about what drugs or health technologies to fund, could be informed by CPGs recommendations. These decisions, in turn, can have a direct impact on what can transpire within the clinical encounter. For example, failure to fund medications or drugs in a publicly funded system likely will reduce the care options offered to patients, even if CPGs recommend their use. Also, quality improvement activities at a hospital level can lead to monitoring and audit of practitioners' adherence to the CPGs. Feedback can emerge from these activities, which will very likely influence future practitioners' behavior and their adherence to CPGs recommendations. Thus, CPGs have the potential of informing other actions or decisions points that may in turn, influence the decisions made at the clinical encounter.

Further, considering CPGs development process - a comprehensive review of the evidence, which is analyzed in detail by a multidisciplinary group of experts, and leads to contextually relevant recommendations - may be useful to activities that are not directly related to health care decisions. For instance, medical schools and hospitals are interested in training future doctors and residents with the best knowledge so they can apply this knowledge to their patients. CPGs may be useful tools to inform medical education and facilitate the education process by providing current recommendations and current summary of the best available evidence (15, 16). Also, CPGs have the potential to identify areas in which there are significant and relevant research gaps that may need to be addressed. This potential could be useful for prioritizing topics and allocating research funding (17). Lastly, it has been described as well, how courts might use CPGs recommend in a specific clinical scenario as a standard of care in cases of malpractice litigations (18). Therefore, other areas, not directly related to health care, have also taken advantage of the CPGs.

Being clinicians the first intended users of CPGs, they have been the natural target of recommendations' use but also the focus of research study on CPGs use. In the last two decades, significant amount of literature has emerged trying to understand what the best ways are to get the CPGs used by clinicians and what are the barriers and facilitators of this use (19, 20). In contrast, although there is acknowledgement of the other roles the CPGs play and the potential implications of their impact on clinical encounter, this has been poorly studied. Specifically, it is not clear what are the roles of CPGs outside the clinical encounter, how frequent CPGs play these roles, how CPGs are they used to inform them.

Examining the role of CPGs in activities and decisions outside the clinical encounter is important for CPGs developers, decision-makers, and even clinicians. Understanding whether these roles are frequent, how CPGs inform those decisions and determining the barriers and facilitators for these roles, can have a strong impact on CPGs implementation and development, and also on the designing of CPGs development programs. Identifying these roles will provide insights and facilitate the discussion among developers and decision-makers about the intended target of their CPGs, and how they can be better developed to make them more useful. Alternatively, even if for some developers their CPGs are only intended to inform the clinical encounter, defining all the other potential these roles may be crucial to establish limits about the context in which their recommendations are intended to be used. Finally, defining and understanding these roles will facilitate researchers in the designing of studies aiming to develop new methodologies for enhancing these roles or improving CPGs format to make them fit to these roles, if needed.

I designed this thesis project to provide some answers to these questions with the aim of generating some theoretical foundation on the scope of guidelines and all their potential goals. The questions that support the development of this thesis were focused on the need for determining what those roles of the CPGs outside the clinical encounter are, how frequently they occur, and how, and under what conditions CPGs are used in these roles. I am convinced that all CPGs developers and researchers should reflect on

these questions before undertaking a guidelines project or before designing new research on CPGs methods.

Thesis goals and scope

This dissertation focuses on understanding the roles of CPGs in decisions and activities outside the clinical encounter. Specifically, this dissertation had the following specific aims:

- Identifying what are the different roles CPGs play outside the clinical encounter and understanding how, and under what conditions CPGs are used in these roles (Chapter 2).
- Describing the roles of CPGs outside the clinical encounter, and the frequency of these roles from the perspective of international CPGs developers (Chapter 3).
- Understanding whether CPGs play a role in drug funding decisions, and how, and under what conditions, CPGs have been used in this role in two different settings (Colombia and Canada/Ontario) (Chapter 4).

In Chapter 2, I report my first study which was a critical interpretive synthesis (CIS). In this study I extensively review the literature with the aim of highlighting and classifying range of activities in which CPGs play roles beyond the clinical encounter. Using these data, I developed an explanatory framework that describes what roles are reported in the literature, another framework to determine how CPGs are operationalized in these roles and described under what conditions these roles are in place. I also summarized those roles in which there is a need for further research focused on the development of tools to facilitate the link between the recommendations and each role.

In Chapter 3, I present my second study which was a cross sectional study. In this study I conducted a global survey, which was built according to the CIS results, focused on the organizations or groups that regularly produce CPGs. Using the results of the CIS study, I conducted an on-line survey of

the international CPG development community. I described how frequent each of the roles are reported by the CPGs organizations and how frequent developers consider the stakeholders in charge of those activities are considered as target users of their CPGs.

In Chapter 4, I present my third study, a multiple case study. In this study, I focused on one of the main roles of CPGs outside the clinical encounter, drug funding coverage decisions. I chose this role because I was interested in gaining in-depth understanding of one of the main roles (quality of care and economic decisions). The role on economic decisions, and specifically drug funding decisions, emerged in the CIS and was frequently endorsed in the survey study. Therefore, I designed a case study to understand whether CPGs are used for drug funding decision-making, how CPGs are used for this role and under what conditions CPGs play a role in these decisions, in two specific jurisdictions: Colombia and Canada/Ontario.

In Chapter 5, I integrate and conclude this work. In this section, I summarize the principal findings, the strengths and limitations, and the implications for research, practice and policy. Specially, I provide an overview of the thesis and how the results from each study come together to provide final remarks.

Lastly, although each one of the three studies present a unique research contribution based on specific research questions, they are part of an integrated program of research intended to answer a big overarching question: how CPGs play some roles outside the clinical encounter. Therefore, the three studies are closely linked and integrated to respond this question and provide an overview that goes from the literature, to a description of the current status from the developers' perspective and provides a deep analysis of one of the roles. This integration is clear strength of this work and makes these results trustworthy. To complete this program of research, the in-depth study of the other main role (quality), or is secondary roles (e.g., education or research prioritization), might be needed to continue increasing the knowledge of the role of CPGs outside the clinical encounter.

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CHAPTER 2: IDENTIFYING THE ROLES OF CLINICAL PRACTICE GUIDELINES IN HEALTH CARE DECISION-MAKING BEYOND THE CLINICAL ENCOUNTER: A CRITICAL INTERPRETIVE SYNTHESIS

Chapter 2. Identifying the roles of clinical practical guidelines in health care decision-making beyond the clinical encounter: a critical interpretive synthesis

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Abstract

Introduction: clinical practice guidelines (CPGs) are evidence-based guidance tools, which are mainly focused on supporting decisions involving clinicians and patients. However, CPGs have been increasingly used by additional stakeholders to inform and support decisions and activities beyond the clinical encounter. Our objective was understanding how, and under what conditions, are CPGs used for decision making outside the clinical encounter.

Methods: A critical interpretive synthesis approach was used. We searched eight different databases up to March 2019, to identify all empirical and non-empirical articles that focused on the role of CPGs outside the clinical encounter. We considered articles that reported, described or recommended the use of CPG in different activities, or reported on methods or the development of tools, or reported or discussed facilitator and barriers of the use of CPGs. Two reviewers independently screened records and assessed for inclusion. One researcher conceptually mapped the included articles. We thematically synthesized the results and developed an explanatory framework.

Results: We included 220 articles. We developed a framework to explain how CPGs play different roles outside the clinical encounter. Based on the frequency and importance of these roles in the health care decisions, we defined three categories: the main roles (informing activities focused on the quality of care and economic decisions), the secondary roles (medical education, maintenance of certification and licensing, and research prioritization), and an unanticipated (judicial decisions). We identified some methods and tools that explain how CPGs play roles on the development of quality indicators and the generation research prioritization lists. We also describe the conditions that facilitate these roles (in general) and some factors that have been barriers for them.

Discussion: CPGs play several roles outside the clinical encounter. We have highlighted what we considered might be the main and the secondary roles, and an unanticipated role. The methods how CPGs play these roles have been studied mostly for developing quality indicators and for research prioritization.

There are not methods or approaches on how CPGs can inform other roles such as in economic decision, activities related to education, certification and licensing or judicial decisions.

Background

Diverse types of evidence-based guidance tools are used in health care decision-making at different levels. Health technology assessment (HTA) and health systems guidance (HSG) are examples of evidence-based documents used by decision-makers to address health systems challenges. HTA are documents that inform payment decisions regarding new technologies to be covered or funded by a health care system or by a health insurance plan. On the other hand, HSG provides support to decisions about health system governance or financial arrangements; or choices among health service delivery options (1)

In contrast, clinical practice guidelines (CPGs) are evidence-based guidance tools that are mainly focused on supporting decisions made between clinicians and patients, such as choosing the most appropriate intervention or diagnostic procedure for the individual patients (2, 3). However, CPGs have been increasingly used by additional stakeholders in the health systems. Recommendations from CPGs may guide quality improvement processes, inform drug coverage and reimbursement decisions, help in the identification of health research gaps, among others (4-7). Since CPGs are based on the best available evidence, they are expected to provide a credible course of action, hence, they could be a helpful tool for varied types decision-makers when considering decisions related to clinical activity in the broadest sense.

While CPGs use, adherence and implementation among clinicians have been extensively studied, the roles of CPGs outside the clinical encounter have not been studied. Given the lack of theoretical development in this field, this review focused on identifying what the different roles CPGs play outside the clinical encounter are, and how, and under what conditions CPGs are used. Understanding the potential uses of CPGs by different stakeholders will improve the knowledge about the potential impact

of CPGs in health care decisions and can also provide insights about the best way to develop and to disseminate better recommendations that may lead to increased benefits on the patients and populations.

Methods

We used a critical interpretive synthesis (CIS) approach to synthesize the available literature (8). The CIS is an adaptation of meta-ethnography that draws on analytic techniques from grounded theory (8, 9) and it is considered an appropriate approach for research questions that need to draw on a heterogeneous body of literature that may not be well developed or focused. CIS facilitates the analysis of complex and diverse bodies of literature including qualitative, quantitative and theoretical papers (8), and it aims to generate a theory based on the interpretations of different sources of evidence (9). This protocol was registered at the PROSPERO database (CRD42017065134). As proposed by Dixon-Woods et al., we adopted a "compass" question to underpin the design and conduct the review(8). Our compass question was: what roles CPGs play in decision-making outside the clinical encounter, and how, and under what conditions are they used in these roles?

Literature Search

We searched in Medline, EMBASE and Health Star (all via Ovid), Health Systems Evidence, CINAHL, LILACS and Web of Science, from inception to May 2019. The detailed Medline strategy is provided in Appendix 1. The search combined terms related to the main area of interest (i.e., guidelines) with terms related to the potential guidelines uses (i.e., roles, uses, reimbursement, coverage, benefit plans, payment, quality improvement, quality assurance, health insurance, legislation, education, professional standards, research gaps or priorities, among others). Additional searches focused on specific websites identify published and unpublished literature were performed. We did not apply any restrictions by language, study design, type of publication, or time period. We conducted additional purposive searches to identify literature to fill conceptual gaps that emerged during our inductive process of

synthesis and analysis again during our inductive constant comparative approach to analysis of the included papers.

Eligibility criteria

We included all empirical and non-empirical articles that focus on CPGs use beyond the clinical encounter. Regardless of the design or the type of publication, we considered all articles that: 1) reported, described or recommended the use of CPGs; 2) reported on methods, approaches or tools for using and/or adapting CPGs in any scenario; or 3) reported or discussed barriers or facilitators of the use of CPGs outside the clinical encounter. Studies needed to be focused on CPGs, which are defined by the National Academy of Medicine (formerly, Institute of Medicine) as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"(3). Papers focused exclusively on the use or role of HSG, policy briefs or HTA were not be considered, unless they explicitly refer to their relationship to CPGs. We defined clinical encounter as the decision-making by clinicians that have direct impact on their patients during a clinical encounter.

Reference reviewing and article selection

We reviewed titles and abstracts of all references retrieved. Each reference was assessed in duplicate by two researchers (IDF & CMV). References were classified as "potentially relevant" or "exclude". We then retrieved the full text of all the potentially relevant articles flagged by at least one of the reviewers, and reviewed them independently, and in duplicate, to make a final assessment for whether they were eligible or not. Disagreements were resolved by discussion.

Data extraction and conceptual mapping

We conducted a conceptual mapping and data extraction using a structured form (Appendix 2). This form was used to guide the extraction but as the results were emerging and the categories were

created, the form had to be adjusted according to new data that was needed from the papers that provided the richest information. Included documents were categorized and conceptually mapped according to the following categories and variables: Study characteristics (including bibliographic details, setting/country), type of paper, scope, activities in which CPG play potential roles (quality improvement, financing decisions, reimbursement, coverage, benefit plans, professional standards, educational decisions, and identifying research gaps), how guidelines play a role on the mentioned activities (description or development of methods, approaches and tools used for these roles), and under what conditions CPGs play those roles.

Synthesis of findings

We used qualitative methods to analyze and synthesize data. Although we aggregated the data, the primary function of the CIS was interpretation. A constant comparative method throughout the analysis to develop an explanatory framework of what re the roles, how and under what conditions CPGs play roles outside the clinical encounter. The following iterative steps were carried out: identifying common themes and concepts based on our summaries and data extraction from each paper; developing theoretical constructs based on the emerging themes and concepts; critiquing the emerging theoretical constructs and identification of the conceptual gaps in the literature in relation to our objectives; conducting additional purposive sampling of included papers and/or conducting additional purposive searches to fill conceptual gaps until theoretical saturation was reached; and integrating the theoretical constructs into a 'synthesizing argument' about what are the roles, how they are played and under what conditions (i.e., an explanatory framework)(9).

Results

We retrieved 19,488 references from databases, and after duplicates removal, we obtained 16,430 references. We excluded 15,894 records due to lack of relevance and duplicates, and 536 were considered potentially eligible, and thus, were reviewed in full text. We excluded 327 studies with reasons, and we

included 209 studies. Appendix 3 displays the selection process, and appendix 4 details the excluded studies. After additional manual and targeted searches performed once we had a map of the evidence, we retrieved 11 additional papers. We included 220 papers (See appendix 5 for details of included articles). Most of the included articles were non-research papers (75.1%), and they were published between 1987 and 2019. More than half of first authors' articles were from the US (56.8%), followed by the UK (14.6%), Canada (6.6%), Netherlands (2.8%), Germany (2.8%), and others.

Framework: Role of CPGs outside the clinical encounter

Arguably the central role of CPGs is to inform the decisions at the level of the clinical encounter. However, they play crucial roles in supporting decisions at different health care system levels and even in other fields. We identified many roles and we grouped them into three categories according to how important and frequent these roles are for decisions in health care: main roles, secondary roles, and unanticipated roles. The main roles (quality of care and economic decisions) are those that we more frequently identified in the literature, they have been described as goals of CPGs development, they may have substantial impact on health care decisions, and they might even explain the rise of CPGs in the last decades in different health care systems(10).

Secondary roles (medical education, certification and licensing, and in research prioritization) are those activities less frequently described in the literature, that do not have a direct impact on health care decisions, for which CPGs may not be the initial target of recommendations, and thus, not the direct aims for developing recommendations. A final category was we defined as an unanticipated role (judicial decisions), to define an activity that is not an aim of developing CPGs, they have no impact on health care decisions and, but still is described as a common role. Table 1 summarizes our framework. We present below the details of each role.

Main role 1: Quality of care

The roles of CPGs in quality of care includes the development of standards and indicators, facilitating quality improvement initiatives and clinical governance, and supporting accreditation and services' certification activities.

Developing quality/clinical standards and quality indicators

A quality or a clinical standard is an agreed process that should be undertaken or an outcome that should be achieved for a particular circumstance, symptom, sign or diagnosis (or a defined combination of these). It should be evidence-based, specific, feasible to apply, straightforward and unambiguous to measure, and produce a clinical benefit and/or improve the safety and/or quality of care, at least at the population level (11).

Indicators are defined as explicitly defined and measurable items which act as building blocks in the assessment of care (12). Indicators can measure structures, processes, and outcomes of care (13). Quality indicators are considered the measurable component of a quality standard with explicit criteria for inclusion, exclusion, time frame and setting (11). Quality indicators are commonly used to monitor CPGs use by health care workers. They can be provided by the CPG s(14, 15), or they can be developed from recommendations(16, 17). The role of CPGs in quality indicators and quality standards development has been highlighted as a key one (12, 16-21).

Facilitating quality improvement initiatives and clinical governance

The central component for improving quality through CPGs is disseminating and implementing them. However, implementation efforts are usually conducted by organizations that have previously established quality improvement (QI) initiatives. Several authors have suggested that there is a need for enhancing the relationship between the CPGs and the local QI initiatives to guarantee success in both

activities (22). Additionally, CPGs have been found useful in identifying processes of care that are of interest for clinicians (23) and in highlighting important patient outcomes to incorporate them in patients' satisfaction surveys(24).

Clinical governance is a "framework through which the [UK's] National Health Service organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish (25, 26). Some clinical governance frameworks require organizations to facilitate the implementation of CPGs and monitor their use (27). Thus, clinical governance provides the structure to enable a successful implementation of CPG recommendations.

Evaluating decisions on health services organization

Groene et al. described the usefulness of CPGs to evaluate the impact of changes in the health services organization and structure (28).

Supporting accreditation and certification programs

The Joint Commission on the Accreditation of Healthcare Organizations selects some CPG-based measures to assist in the accreditation process and institutions must articulate how CPG-based measures have been met and should make efforts to mitigate factors that may explain lack of adherence (29). Some evidence has shown that fully accredited hospitals are more likely to follow CPGs' recommendations in comparison to partially accredited hospitals (30). Also, CPGs have been used to support hospital disease-specific care certification programs (31, 32).

Main role 2: Economic decisions

The roles identified under the goal of economic decisions are informing coverage or reimbursement decisions, supporting health care rationing and cost-containment policies, suggesting how to allocate health resources, and supporting financial incentives strategies.

Informing coverage and reimbursement decisions

CPGs can help in determining what should be included in insurance coverage or benefit packages (drug funding decisions) (33-35), regardless of the type of the health care system. CPGs have been considered excellent tools to determine 'what works', which in addition to costs considerations in general, and cost-effectiveness analyses (CEA) in particular cases, allow policymakers to determine the value for money of services. There are some cases in which economic analyses are performed within the CPG, or developers use available CEAs from the literature or the context, to inform the recommendations (34, 36, 37). However, most CPGs do not consider CEA, and their recommendations are mostly driven by the effectiveness and safety evidence. Nevertheless, these recommendations can inform other processes in which CEA are developed by other actors for specific contexts, such as in cases of HTAs (38, 39).

Informing health care rationing and cost-containment policies

CPGs can be acceptable tools for health care rationing if they are developed with the highest standards and stating explicitly the rationale behind the decisions taken during their development (40). Health care rationing is a positive concept considering the scarcity of resources and the need for targeting those resources to obtain the best value for money (41). However, some authors have raised concerns about the related terms 'cost containment' and 'cost-cutting'. In this case, CPGs are used "in the name of quality", but they are seen as an imposition from managers and policymakers to reduce health care costs and restrict services regardless of the impact on quality, namely, just as a cost-containment tool(22, 42).

Informing health care resources allocation

CPGs may inform decisions by policymakers that are allocating health care resources, because stating what the best treatment approaches are, should facilitate decisions regarding the allocation of personnel, hospital beds, and other resources (43, 44)

Supporting financial incentives strategies

Financial incentives, either positive (rewards) or negatives (penalties), are aiming to impact the performance of organizations and physicians. CPGs recommendations are used as benchmarks to define ideal care. Pay-for-performance (P4P) emerges in response to the mentioned increase in health care costs in the eighties and nineties in the US (45). Voices against this role come from clinicians and professional societies that argue that P4P create incentives on physicians that focus on certain diseases and could negatively impact the quality of care (46, 47).

Secondary role 1: Medical education, maintenance of certification and licensing

CPGs have played roles in informing medical education, continuing medical education (CME), and licencing and maintenance of certification (MOC) processes.

Informing medical education and residency training

Some reports put CPGs as an essential teaching tool that should be considered as one of the best practices in health (48, 49). Surveys have shown that US residency programs are commonly teaching about searching and critically appraising CPGs (50). CPGs are used for discussion in didactic lectures (51), as a framework to conduct peer review assessments, and as focused evaluations in specific diseases (52, 53). This role seems to be rooted in need for increasing the use of CPGs, and in pushing implementation activities, and in the notion by educators that CPGs improve the quality of care (54).

Supporting continuing medical education (CME) activities

CPGs may support CME activities, such as formal conferences, courses, symposia, workshops, or small group discussions(29, 51, 55). CPGs are perceived as useful for providing grounds for discussion of contemporary patient management in clinical (inpatients' rounds) (51) or educational (e.g., didactic lectures) settings. CPGs are recommended to identify competencies to guide CME assessments.

Supporting licensing and maintenance of certification

Licensing involves the definition of minimum standards of competence for a specific field. Weisz et al. argued that the need for standardizing along with the need for providing benchmarks for licensing had also contributed to the expansion of the CPGs in the US (10). The maintenance of certification (MOC) is a regular assessment required for board certification of medical specialities. MOC procedures in North America use web-based modules for physicians' self-assessment, to compare their knowledge with peers and against benchmarking of best practices, and to receive feedback. CPGs inform the development of these modules (56, 57).

Secondary role 2: Research prioritization

CPGs are a good source of research gaps which may be useful for researchers and funding agencies (43, 58-60). The prioritization process can occur during their development or after publication.

Generating a list of research priorities (post-publication)

In this case, CPGs play a passive role. Researchers or funders can review already available CPGs and identify topics in which there was no evidence, or this was of low-quality or not relevant, to support the recommendations. These topics will eventually become areas where further research is needed and should be prioritized.

Creating specific recommendations for future research (during development or pre-publication)

CPGs can also play a more active role if during the development developers explicitly develop statements that highlight the gaps, using terms as "further research is required" or "research gaps" that are found in the CPG document. Moreover, in some cases, there could be specific "research recommendations". This role requires establishing this activity as part of their development methods.

An unanticipated role: Judicial decisions

CPGs have informed courts' decisions in cases of malpractice litigations and coverage disputes. Although unanticipated, this role might not be uncommon.

Acting as inculpatory or exculpatory tools

The role of CPG in malpractice litigation as an inculpatory tool, or as a "sword", means that plaintiffs use them in an attempt to prove that a defending physician has deviated from what should be considered the standard (CPG recommendation). On the other hand, defendant physicians may use CPGs to demonstrate that they followed the standard of care, i.e., as exculpatory tools, or as "shields" (61). Some reports have described that the use as inculpatory tools is much more common than as an exculpatory tool (62). Although CPGs are not mandatory standards to follow, it is accepted that physicians should be aware of the most accepted recommendations and deviation from them should be supported on a convincing rationale (52).

Informing coverage disputes

A particular situation to mention is the role of CPGs in informing courts in cases of coverage disputes to determine whether a service should be or not covered by a health system or benefits package (63, 64). However, there has been some discussion about the suitability of CPGs for this role (65).

How CPGs play these roles?

We identified some evidence on how CPGs play some of the mentioned roles. We grouped the methods and approaches as occurring post-publication (i.e., using already available CPGs), or pre-publication (i.e., process led by the developers to generate statements or specific outputs that may inform the role).

Some methodologies that facilitate the post-publication approach of moving from recommendations to developing quality indicators have been described (66, 67). Kotter et al.(68) summarized a wide variety of methods but did not find evidence on which or which ones could be the best methods. Recently, Langendam et al., summarized the all the current approaches and found that most of them were post-publication, and there is a lack of information on how to integrate better the development of both indicators' and CPGs development (69). Parmelli et al. recently developed a framework to integrate both processes (pre-publication approach) through the development of indicators and performance measures from the outcomes covered by the CPGs (70). We did not find specific tools or methodologies (pre- or post-publication) to facilitate the link between CPGs and accreditation or services certification activities.

We found some models that point out how CPGs are the first stage in the evidence assessment of health technologies that may be followed by economic and ethical analyses, to develop a full HTA (post-publication) or experiences for collaborative work between CPG and HTA (pre-publication) or development of CEA as part of the CPG development (i.e., NICE experience in the UK)(71). However, there are no specific tools (pre- or post-publication) to integrate better CPGs with HTA to inform coverage decisions.

Regarding how CPGs produce health care rationing, it seems to be an indirect effect due to the reduction in the variability of health care practice, a reduction in the use of expensive and ineffective services. Thus, CPGs produce "implicit rationing" by encouraging physicians to make more rational decisions (72). Lastly, for P4P activities, the described approach is to prioritize recommendations from high-volume conditions and monitor the adherence through indicators, allowing comparison of performance, and the provision of financial bonuses to the best-ranked physicians or organizations (73). We did not find specific pre- or post-publication methodologies to inform this process.

We failed to identify any methodologies (pre or post-publication) to facilitate the use of CPGs as educational tools. For instance, it is not clear how CPGs might inform the development or updating of

medical schools' curriculums or how they can better support clinical trainees' evaluations. We also failed to found methods to link CPGs to licensing and MOC activities. Regarding CME, there is plenty of literature describing that CME is an effective intervention to enhance adherence to CPGs (74). This evidence mostly driven by CPGs' implementation projects, and in these cases, CME is the tool to implement the CPG and CME is not a goal of the CPG itself (post-publication approach).

We identified some approaches to facilitate the role in informing research prioritization activities. For the post-publication role, we found several examples and methodological approaches. Most of them involve the searching and identification of CPGs and generating lists of priorities (including topics to develop HTA) through non-systematic approaches (75, 76) or consensus-based methodologies (77-82), usually focused on recommendations with low-quality evidence (77, 79, 81, 83, 84). In the pre-publication approach, developers should explicitly highlight the areas that require further research (e.g., when there is low quality evidence or no evidence at all), by developing 'research recommendations' or 'further research' statements (78, 82). Moreover, developers may go beyond and can even suggest the how to fill that gap (i.e., what study design should be done, or in what specific populations)(85, 86). For instance, Sharma et al. summarized a collaboration process between NICE and the National Institute for Health Research (NIHR) in the UK, using CPGs (which include "research recommendations") and HTA (87). However, to date, there is no specific guidance or tools on how to develop these statements, how to prioritize these gaps, what is the best format to present this information, and how to reduce the gap between the CPG and the potential funders (88).

We did not identify approaches that may explain how CPGs may inform better judicial decisions either in malpractice litigations or coverage disputes. Figure 1 displays the status and the gaps on available approaches and tools to link CPGs better to the roles.

Under what conditions?

There are some conditions that facilitate the roles of CPGs, and some others were found as barriers. Figure 2 summarizes the general and role/specific facilitators and barriers.

Facilitators

We identified that the need for improving quality and containing health care expenditure, the evidence-based nature of the CPGs, the advantage of saving time and resources, and the characteristics of the developer, have been facilitators of the CPGs roles.

The emergence of a greater focus on improving quality of care and controlling health care expenditure was a major facilitator of CPGs main roles. There was a need for regulating quality in the US in the 1980s and 1990s, which led to the introduction of CPGs into the management models for quality assurance (10, 89-91). Later, the literature shifted into the potential role of CPGs in 'quality improvement'(22, 92, 93), while more recently (mostly in the UK) into their role for developing 'quality standards(17, 94-96). Simultaneously, the need for controlling health care expenditure promoted their role in economic decisions (10, 97). CPGs were ideal tools for this role as they recommend the necessary medical services, and therefore, they can indicate what to pay for (42, 98). In the US, the creation of the Agency for Health Care Research and Quality (AHRQ) was the start of the US government involvement in the CPGs development (10), with the aim of improving quality and controlling costs (99). The creation of NICE in the UK also was driven by the need for improving quality of care, but also considering cost-effectiveness. Although in both countries, the quality goal was always accompanied by the costs' dimension, in the latter, there was a much stronger government participation, and CEA was introduced as a key element to complement effectiveness assessment.

A condition that has become a key facilitator of all the roles of CPGs is the systematic and evidence-based methodology followed for their development. Users (policymakers, insurers, managers, among others) took advantage of the fact that CPGs became evidence-based tools and that most of the resources and that the specialized-skilled work required for synthesizing the evidence has already been done, and saving time and resources(48, 52, 100, 101). Also, the acceptance by the general public of CPGs as a useful tool for informing coverage decisions(33) and for controlling health care expenditure without sacrificing quality, if both, quality and costs, are considered together during their development(102) are conditions that have facilitated their role in economic decisions.

Lastly, a condition that impacts on how significant these roles are, is the developer's characteristics and purpose. Government-funded organizations might be more interested in creating implementation tools and providing quality indicators and quality standards, or to be used in economic decisions. In contrast, professional societies' CPGs might be more focused on informing the clinical encounter, and in setting their own professional standards than in informing economic decisions (89, 103, 104).

Barriers

Among the barriers that, in general, affect the roles of CPGs outside the clinical encounter we found: the lack of availability of CPGs for all the conditions of interest, the high requirements needed for their development (costs and technical capacity)(105-107), the lack of appropriate quality standards of many CPGs (including differentiating evidence from opinions)(46, 102, 103, 108-110), and the inappropriate management of conflicts of interests(45, 46, 100, 106, 111-113).

Specific barriers found for the role of CPGs in quality of care activities include: low quality of evidence upon which to make recommendations(114), the risk of recommendations rigidly enforced by managers(115), lack of available CPGs for all the topics(116), the need for implement modifications on the recommendations to develop indicators, the lack of guidance to do this(66, 93, 95, 116-118), and the lack of costs considerations during the CPG development(114). The most important barrier found for the

role in economic decisions was the lack of inclusion of costs and CEA(109, 119-121). Also, the fear of using CPGs for economic decisions may be that clinicians will consider them as a cost-cutting, rather than an efficiency tool (122).

Time constraints, lack of interest from residents, and the fear that CPGs may constrict the teaching environment, the fear of offering cookbooks approaches to trainees, which may affect "the development of a trainee's curiosity and creative skills", and the use of low-quality evidence to support educational activities, are some of the limitations of CPGs as educational tools (50, 53, 54, 123). We did not identify specific barriers related to their role as research prioritization tools.

Among the barriers for the role on judicial decisions, we found: the existence of conflicting guidelines (113), lack of guidance on how to select the best CPG (124), and the low quality of many CPGs(111, 125). Clinicians, meanwhile, fear that the lack of adherence to CPGs may result in an increase their exposure to litigations (126).

Discussion

Principal findings

We have extensively reviewed the literature to highlight and classify many activities in which CPGs play roles beyond the clinical encounter, and we developed an explanatory framework that describes what roles are and explains how and under what conditions. We argue that CPGs have two main roles (quality of care and economic decisions), two secondary roles (educational, certification and licensing, and research prioritization), and one unanticipated role (judicial decisions).

For some roles, we found some methodological approaches or tools that facilitate them. For instance, some frameworks for developing quality and performance indicators from CPGs, and for

developing research priorities lists from CPGs have been reported. However, no tools or approaches to support the roles on economic decisions, educational activities and judicial decisions were found.

The conditions that worked as facilitators for these roles were the historical need for improving quality and containing health care expenditure, the evidence-based nature of CPGs, the opportunity to save time and resources and the developers' characteristics (government-funded vs other types of organizations, such as professional societies). In contrast, conditions described as barriers were: high development requirements, lack of conflicts of interest management, low-quality methodological standards (in general); the low quality of available evidence, lack of enough CPGs, the lack of guidance to link recommendations to some roles (quality of care); the lack of appropriate considerations of costs and cost-effectiveness in the CPGs development, and the perception of CPGs as a cost-containment tool the high requirements for development (economic decisions); the lack of interest, the use of low-quality evidence and the perception of CPGs as a cookbook (medical education); and the existence of conflicting guidelines, and the lack of guidance to select the best CPGs (judicial decisions).

Lastly, it should be noted how, in the last decade, enormous methodological advances have emerged in the CPGs field. As a result, some of the highlighted barriers, such as the lack of appropriate methodological standards, the lack of consideration of costs, and the need to control conflicts of interest, may have been reduced or eliminated, in many cases. More research on these barriers focused on specific roles might help in defining the real impact of some barriers in current days.

Findings in relation to other studies

We identified neither an evidence synthesis nor a framework development paper on the potential roles of CPGs. Most of the available literature that discusses the roles comes from narrative reviews, discussion papers, or editorial letters. Interestingly, many conceptually important papers that are narrative reviews and debate papers from the 1990s or early 2000s. Classical and influential articles from authors such as Eddy(98), Grol(127) or Woolf(4, 60, 128, 129), describe most of the roles we have summarized

here. These articles are among the most cited ones, and many major roles and uses of CPGs have been supported on them, for decades. However, these papers do not provide empirical evidence on how frequent the roles were or how these roles have been put in practice. Some systematic reviews included in our synthesis have focused on summarizing the methods for developing indicators from CPGs (68, 69, 94), but we did not identify any evidence synthesis on the role of CPGs focused on all the roles or on specific ones.

Strengths and limitations

Our review has several strengths. We followed international methodological standards in conducting CIS. We performed a very comprehensive search, in the most important databases in the field, without language or date limits. We also performed manual and hand searches, and we conducted focused additional searches after the main roles were emerging from the first analyses, using more specific terms to identify additional key papers related to specific roles.

However, this review has some limitations. We have developed a search strategy focusing on the studies that emphasized on the CPGs, but also on previously identified roles. However, it is possible that literature on specific roles that we did not anticipate, or in which CPGs were not a prioritized may have been missed. We excluded literature that was focused on experiences with the use of CPGs in specific diseases unless they were very informative on general aspects of the role or provided crucial concepts or methodologies that could be useful for developing our framework. This may have caused that we lost additional evidence.

Implications for policy and practice

Our results will be useful for guideline developers, policymakers and stakeholders. Developers can use our framework to determine what are the potential roles that their guidelines could play in their context. Our findings might be useful for them to focus their CPG development, and this will influence

the definition of the scope and objectives, the questions' definitions, and the potential CPGs users and thus, to better target their recommendations.

Policymakers and stakeholders can consider our framework in several ways. First, when determining potential CPGs programs, as our results could help in designing their scope and the potential users of the CPGs. Also, health managers can understand the scope and the roles of the CPGs recommendations, and therefore, the CPGs usefulness in their contexts. Policymakers at different levels can also identify many additional roles that they were not aware of, on which CPGs can help by supporting economic decisions or informing activities aimed to improve the quality of care. Policymakers in charge of defining policies about health research could find our framework useful as it calls attention to the CPGs as a valuable resource to inform what areas should be prioritized for future research. Lastly, these results can bring awareness to stakeholders in charge of defining medical curriculums, licensing activities and maintenance of certification processes about the role of CPGs on these activities.

Implications for future research

Although the literature describing the potential roles is extensive, there is no evidence on how frequent they occur and is scarce the evidence on how to facilitate the translation process from recommendations to specific roles. Concerning the quality of care, more research for testing the applicability of the available framework that aims to facilitate the collaboration between CPG developers and stakeholders in charge of quality improvement activities is needed. As for the case of economic decisions, further research to understand how CPG may inform HTA and coverage decisions and what are the barriers and facilitators of this role are needed.

Additionally, more research on methodological approaches to facilitate the role of CPGs on educational, MOC and licensing activities, and on evaluating the usability of the frameworks to prioritize researchquestions from recommendations, might be priorities to promote these secondary roles. Also, our framework might be useful for research funding agencies, as we have described ways by which CPGs can

inform the research prioritization process. Finally, future testing of our framework through case studies or other research methods might be good to identify gaps or additional roles to consider. Specifically, identifying new roles that may not be covered by our work might be a priority for further research.

Conclusions

In conclusion, CPGs, although aimed to inform decisions at the clinical encounter, play several roles beyond that level. Main roles of CPGs are related to quality of care and economic decisions, and secondary roles are aimed to support education, MOC and licensing processes, and to identify research priorities. Lastly, an unintended role, the role in the judicial decisions is also described. More research on these roles, such as how frequent these roles occur, and how to improve the link between the recommendations and these roles (particularly for economic decisions and educational activities, and judicial decisions) is needed.

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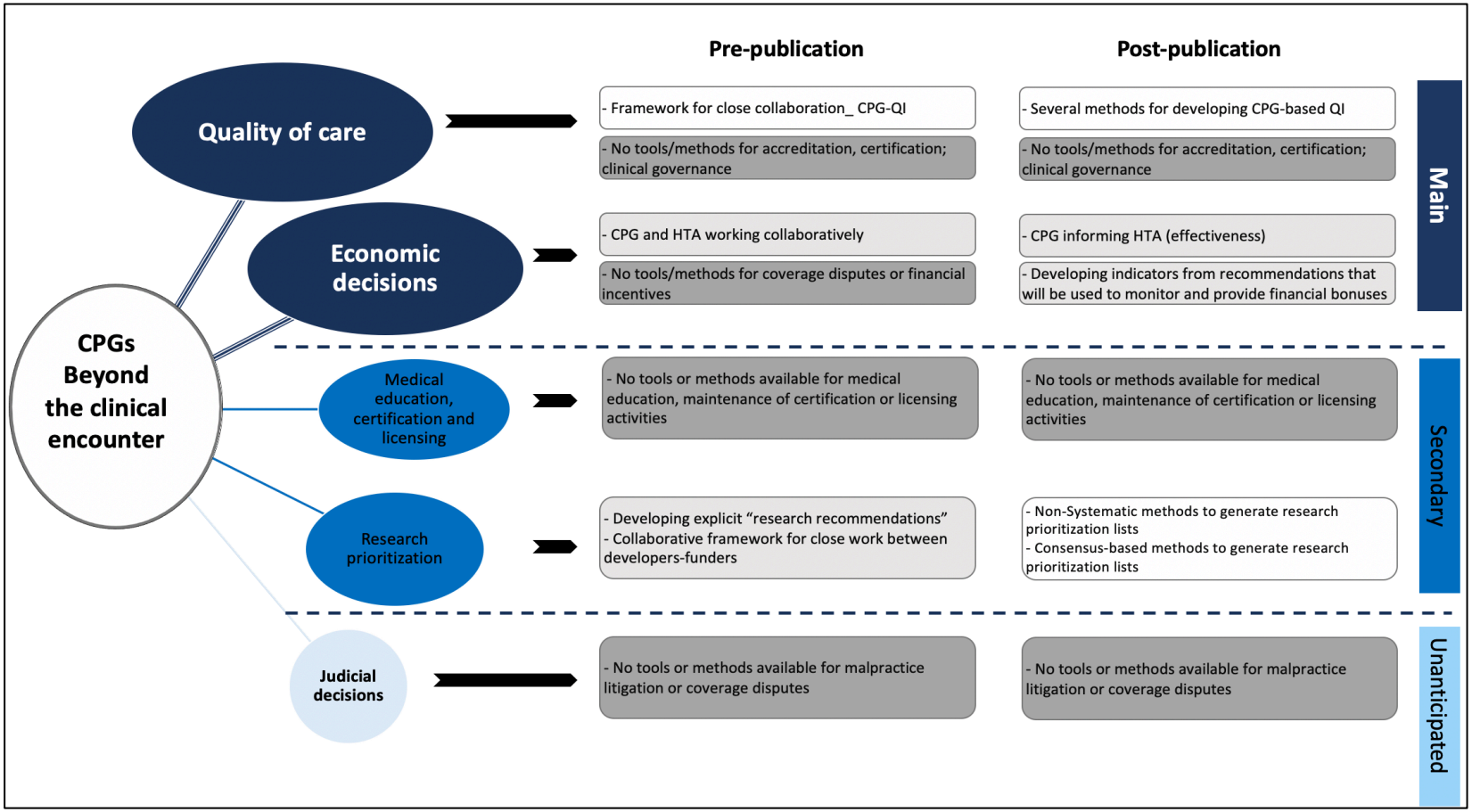
Table 1. Framework for all the roles of CPGs outside the clinical encounter

Type of role	Role's Dimension	Scope	Specific roles	Explanation
Main roles	Quality of care	Informing activities led by managers and policymakers aimed to improve the quality of care in health organizations or health systems.	Development of quality standards and quality/performance indicators	Developing quality standards and indicators for quality improvement or performance measurement initiatives from recommendations
			Facilitating quality improvement and clinical governance	Facilitating process related to quality improvement initiatives, decisions about organization of health care services and activities related to clinical governance
			Accreditation and certification programs	Selecting CPGs and recommendations to monitor use and compare organizations for accreditation purposes. Certifying services in specific diseases management, according to their use of CPGs
			Health services organization	Designing and evaluating changes in the structure of health care services
	Economic decisions	Informing activities to improve efficiency of health systems and organizations, promoting the best value for money	Coverage/reimbursement/drug funding decisions (insurance or public health systems)	Informing (along with economic analyses) coverage decisions evaluations
				Including available CEA (internationally or local analyses) to inform the recommendation that will be used to define coverage
				Developing CEA within the CPG development process to directly inform coverage decisions
			Cost containment tool	Using CPGs to restrict health services without considering quality
			Health care rationing	Using CPGs as a tool for implicit rationing
			Health care resources allocation	Informing health care resources allocation
			Financial incentives strategies	Selecting CPGs and recommendations to monitor use and provide positive or negative financial incentives
Secondary roles	Medical education, certification and licensing	Supporting activities and processes in medical education and licensing	Medical education	Using CPGs to develop didactic lectures
				Using CPGs as benchmarking to compare decisions when evaluating students and residents: Peer-review assessment
				Using CPGs to inform additional specific didactic activities
			Continuing medical education activities	Undertaking workshops, conferences, symposium, in which CPGs recommendations are presented and disseminated
			Licensing and maintenance of certification	Using CPGs recommendation s to develop assessments and examinations
	Research prioritization	Informing the process of research priority setting or gaps in knowledge identification	Research priority lists	Developing lists of research priorities (including HTA topics) from available CPGs based on low quality evidence.
			Research recommendations	Developing of "research recommendations" with information on the designs and populations that are recommended to be studied in future research
Unanticipated role	Judicial decisions	Informing decisions in the courts either inculpatory or exculpatory	Malpractice litigations	Using CPGs an inculpatory tool: By the plaintiff to determine that the defendant physician departed from the standard of care in a judicial process
				Using CPGs as an exculpatory tool: Adherence to a CPGs as a tool of the defendant physician against litigation
			Coverage disputes	Using CPGs as tool to inform courts on coverage disputes.

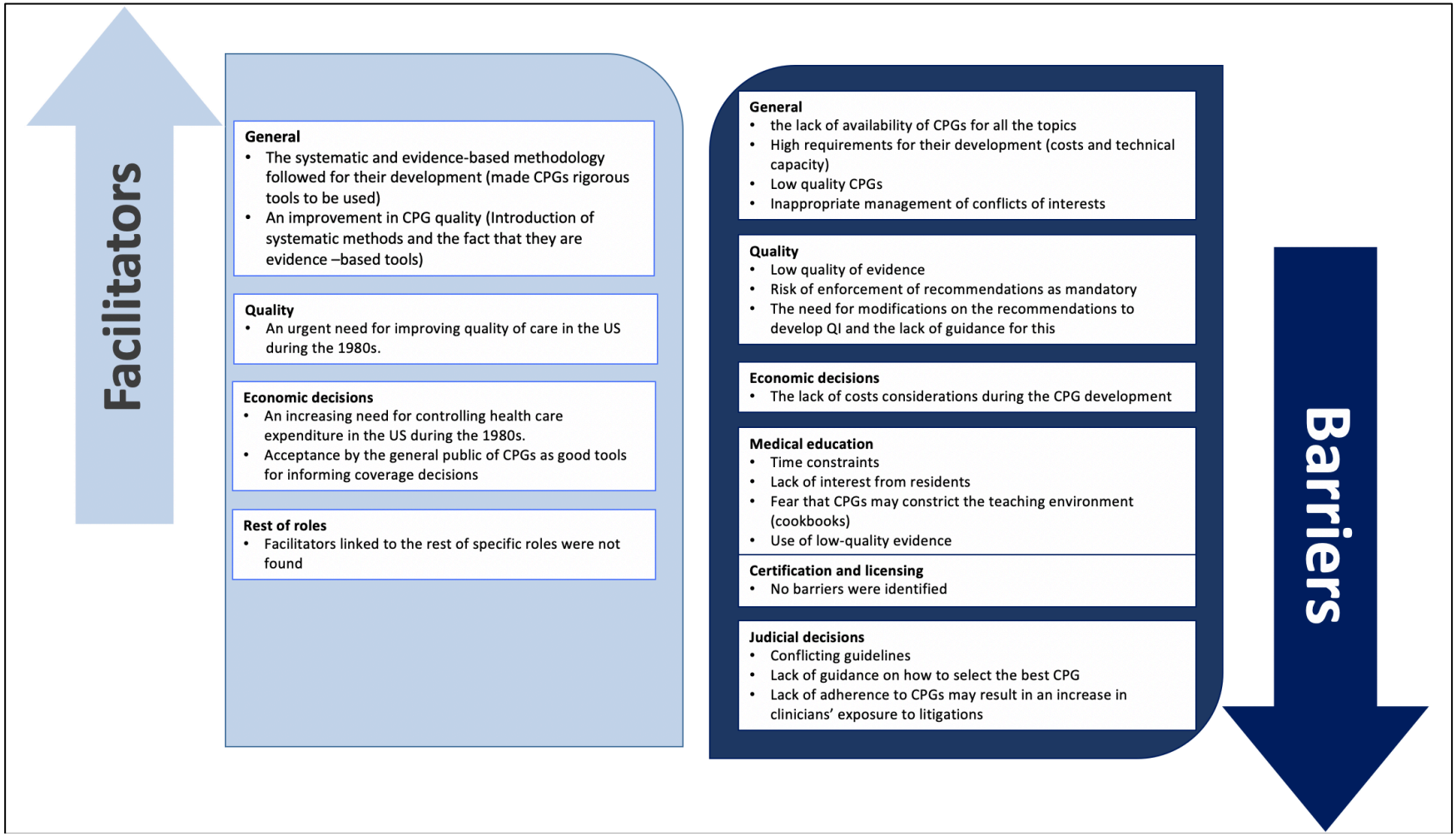
CEA: Cost-effectiveness analyses; CPG: Clinical Practice Guideline; HTA Health technology assessment.

Figure 1. How CPGs play the roles beyond the clinical encounter: Available tools and methods for linking CPGs to specific roles



Methods are categorized according to the stage in which they are applied or developed. ***Pre-publication*** (or during development), as its name indicates, are approaches implemented during the CPG development, i.e., they require their application by developers either as part of their usual methods, or by a close collaboration with others (e.g., quality improvement stakeholders, or drug-funding agencies). Under this approach, CPGs have already incorporated the role as part of their target. ***Post publication*** encompasses the approaches that are implemented with available finished CPGs, usually by CPG users. Under this approach CPGs are not modified, and therefore, their scope and targets are not modified. ***Ovals represent the roles´ categories***; Dark blue ovals represent main roles; blue ovals represent the secondary roles; and, light blue oval represents the unanticipated role. ***The color of the methods boxes represents the status of the available tools and approaches***: A blank box means some tool and approaches have been developed and are available; A light-gray box mean there are some early methods, suggestions, experiences or description in the literature on how this role can be put in practice, but there are no clear methods; and a dark-gray box means we did not identify clear methods or experiences described for a specific role. Abbreviations: CPG: Clinical Practice Guidelines; QI: Quality indicators; HTA: Health technology assessment.

Figure 2. Under what conditions CPGs play roles beyond the clinical encounter: barriers and facilitators to the roles



The figure depicts the facilitators and barriers identified in the literature for all the roles, both, in general and per role. In light blue, the facilitators; in dark blue, the barriers.

Appendices

Appendix 1. Search strategies

Appendix 2 – Data Extraction Form

Appendix 3. Study selection flow chart

Appendix 4. Excluded studies (N=327)

Appendix 5. Included studies (N=220)

Appendix 1. Search strategies

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. Practice Guidelines as Topic/
2. practice guideline$.tw.
3. (clinical adj guideline$).tw.
4. (evidence adj2 recommendation$).tw.
5. CPG$.tw.
6. (PG or PGs).tw.
7. or/1-6
8. (role$ adj4 guideline$).tw.
9. Quality Improvement/
10. Quality Indicators, Health Care/
11. Quality Assurance, Health Care/
12. quality improvement.tw.
13. quality assurance.tw.
14. or/9-13
15. Reimbursement, Incentive/
16. reimbursement.ab.
17. Universal Coverage/
18. Insurance Coverage/
19. (benefit$ adj2 plan$).tw.
20. 15 or 16 or 17 or 18 or 19
21. professional standards.tw.
22. (certification adj examination$).tw.

23. Education, Continuing/

24. or/21-23

25. (research adj3 gap$).tw.

26. (research adj2 agenda).tw.

27. (research adj3 priorit$).tw.

28. or/25-27

29. exp Malpractice/lj, st [Legislation & Jurisprudence, Standards]

30. Judicial Role/

31. litigation.tw.

32. courtroom.tw.

33. or/29-32

34. 8 or 14 or 20 or 24 or 28 or 33

35. 7 and 34

EMBASE (via Ovid)

1. Practice Guidelines as Topic/

2. practice guideline$.tw.

3. (clinical adj guideline$).tw.

4. CPG$.tw.

5. guideline$.tw.

6. PG$.tw.

7. 2 or 3 or 4 or 5 or 6

8. 1 and 7

9. (role$ adj4 guideline$).tw.

10. Quality Improvement/

11. quality improvement.tw.

12. quality assurance.tw.

13. or/10-12

14. reimburse$.tw.

15. coverage.tw.

16. (benefit$ adj2 plan$).tw.

17. or/14-16

18. professional standards.tw.

19. (certification adj examination$).tw.

20. (Continuing adj education).tw.

21. or/18-20

22. (research adj2 gap$).tw.

23. (research adj2 agenda).tw.

24. (research adj2 priorit$).tw.

25. or/22-24

26. litigation.tw.

27. courtroom.tw.

28. or/26-27

29. 9 or 13 or 17 or 21 or 25 or 28

30. 8 and 29

31. limit 30 to humans

HEALTH STAR

1. Practice Guidelines as Topic/

2. practice guideline$.tw.

3. (clinical adj guideline$).tw.

4. CPG$.tw.

5. PG$.tw.

6. or/2-5

7. 1 and 6

8. (role$ adj4 guideline$).tw.

9. Quality Improvement/

10. Quality Indicators, Health Care/

11. Quality Assurance, Health Care/

12. quality improvement.tw.

13. quality assurance.tw.

14. or/9-13

15. Reimbursement, Incentive/

16. reimbursement.ab.

17. Universal Coverage/

18. Insurance Coverage/

19. (benefit$ adj2 plan$).tw.

20. 15 or 16 or 17 or 18 or 19

21. professional standards.tw.

22. (certification adj examination$).tw.

23. Education, Continuing/

24. or/21-23

25. (research adj3 gap$).tw.

26. (research adj2 agenda).tw.

27. (research adj3 priorit$).tw.

28. or/25-27

29. exp Malpractice/lj, st [Legislation & Jurisprudence, Standards]

30. Judicial Role/

31. litigation.tw.

32. courtroom.tw.

33. or/29-32

34. 8 or 14 or 20 or 24 or 28 or 33

35. 7 and 34

36. limit 35 to humans

CINAHL

S8 S6 AND S7

S7 (MH "Practice Guidelines") OR "clinical practice guidelines"

S6 S1 OR S2 OR S3 OR S4 OR S5

S5 AB professional standards OR AB certification* OR AB examination* OR AB education, continuing

S4 AB malpractice OR AB judicial OR AB litigation OR AB courtroom OR AB medicolegal OR AB medico-legal

S2 AB research gap* OR AB research priorit* OR AB research agenda

S2 AB reimburse* OR AB coverage OR AB benefit plan*

S1 AB quality improvement OR AB quality assurance OR AB quality indicators

LILACS (1,055)

(tw:((mj:(guideline*)) OR (tw:(practice guideline*)) OR (tw:(clinical practice guideline*)))) AND (tw:((mj:(quality improvement OR quality assurance OR quality indicator)) OR (mj:(reimbursement OR reimburse OR coverage OR benefit plan)) OR (mj:(research gap OR research priority OR research agenda)) OR (mj:(malpractice OR judicial OR litigation OR courtroom OR medico-legal)) OR (mj:(professional standard

OR certification OR examination OR continuing education)) OR (mj:(role OR roles)))) AND (instance:"regional")

FILTERED By not MEDLINE: #24

Appendix 2 – Data Extraction Form

1. Aim of the study _____

2. **Document characteristics**

i. Bibliographic details [Authors, title, journal, year of publication, issue, number, pages]:

ii. Setting/country

iii. Type of paper (Research/ Non-research)

3. **Methods used:**

a. Primary and secondary research

• Quantitative Research

- Systematic review
- RCT
- Before-after study or Interrupted time series
- Cohort study
- Case-control study
- Cross-sectional
- Cost-effectiveness study
- Other [specify]_____

• Qualitative Research

- Systematic review
- Case study
- Ethnographic study
- Grounded theory study

- Other [specify]
- Mixed Methods Research

b. Non-research

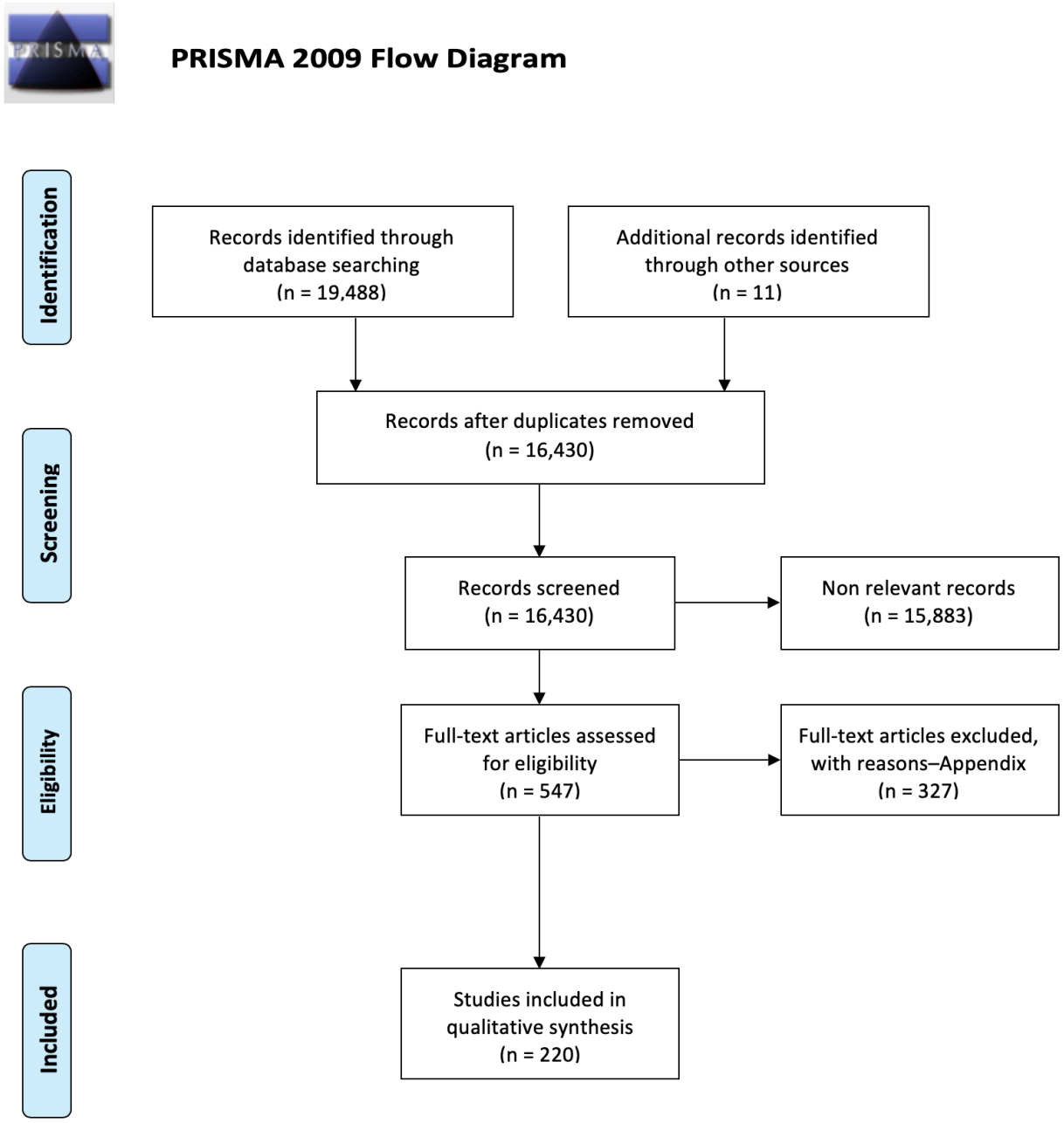
- Theory paper
- Discussion paper
- Commentary
- Editorial or letter
- Health and health system data
- Situation analysis
- Literature or Narrative review
- Framework
- Toolkit
- Guidance
- Government document (discussion/position paper, strategic plan, legislation or policy)
- Other

4. Potential Roles

- Quality improvement&assurance
- Financing decisions (Reimbursement, coverage, benefit plans, etc)
- Judicial decisions
- Professional standards
- Educational decisions
- Identifying research gaps
- Others. Specify _____

5. Barriers or limitation for CPG use outside the clinical encounter, if any
6. Enablers or advantages for CPG use outside the clinical encounter, if any
7. Research needs.

Appendix 3. Study selection flow chart



Appendix 4. Excluded studies (N=327)

1	Abrams GD et al. Quality Measures in Orthopaedic Sports Medicine: A Systematic Review. Arthroscopy 2017	Not related to CPGs or any of the roles
2	Addington D. Best practices: improving quality of care for patients with first-episode psychosis. Psychiatric Services 2009	Not related to CPGs or any of the roles
3	Advani A et al. An intelligent case-adjustment algorithm for the automated design of population-based quality auditing protocols. Studies in Health Technology & Informatics 2004	Not related to CPGs or any of the roles
4	Advani A et al. Intention-based critiquing of guideline-oriented medical care. Proceedings / AMIA 1998	Paper about CPGs in general or about specific topics, not focused on our roles of interest
5	Agarwal N et al. Quality Reporting in Neurological Surgery: Practice Adherence to Quality Payment Program Guidelines. Neurosurgery 2019	Not related to CPGs or any of the roles
6	Akdag HC et al. Improvement of Breast Cancer Patient Pathway Using EUSOMA Standards and European Guidelines. Chirurgia (Bucharest, Romania : 1990) 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
7	Al Mahdy H. Quality assuring adult anti-microbial guidelines. International Journal of Health Care Quality Assurance 2012	Not related to CPGs or any of the roles
8	Al-Adsani A et al. Evaluation of the impact of the Kuwait Diabetes Care Program on the quality of diabetes care. Medical Principles & Practice 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
9	Ales MW et al. Developing and implementing an effective framework for collaboration: The experience of the CS2day collaborative. Journal of Continuing Education in the Health Professions 2011	Not related to CPGs or any of the roles
10	Alexanderson H et al. Disease-specific quality indicators, outcome measures and guidelines in polymyositis and dermatomyositis. Clinical & Experimental Rheumatology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
11	Ali P et al. Criteria based audit in the management of eclampsia at a public sector tertiary care hospital in Karachi, Pakistan. Pregnancy Hypertension 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
12	Amundson G et al. Paying for quality improvement: compliance with tobacco cessation guidelines. Joint Commission journal on quality and safety 2003	Paper on QI/QA or quality indicators, not focused on the role of CPGs
13	Andreeva SN et al. [The analysis of the judicial practice of treating the civil lawsuits concerning	Paper about judicial/malpractice issues, not focused on the role of CPGs

	the inadequate dental health service appeals launched by the patients in the Russian Federation during the period from 1993 to 2017]. Sudebno-Meditsinskaia Ekspertiza 2018	
14	Andrs K et al. Performance improvement with a multidisciplinary clinical guideline for patients undergoing minimally invasive thoracic surgery. Joint Commission journal on quality and safety 2004	Paper about implementation of CPGs (in general or specific cases), not focused on roles
15	Anonymous. Why are physicians subject to clinical guidelines?. Journal of Occupational & Environmental Medicine 2011	Paper about CPGs in general or about specific topics, not focused on our roles of interest
16	Aronow HD et al. SCAI/SVM expert consensus statement on Carotid Stenting: Training and credentialing for Carotid Stenting. Catheterization and Cardiovascular Interventions 2016	Paper on credentialing not focused on CPGs
17	Atienza G et al. [Clinical practice guidelines and primary care. SESPAS report 2012]. Gaceta Sanitaria 2012	Paper about CPGs in general or about specific topics, not focused on our roles of interest
18	Atkins D et al. Broadening the evidence base for evidence-based guidelines: A research agenda based on the work of the U.S. preventive services task force. American Journal of Preventive Medicine 1998	Paper about CPGs in general or about specific topics, not focused on our roles of interest
19	Auger C et al. [Review of reimbursement for instrumental techniques used for assisted coughing and thoracic expansion. A French National Health Authority assessment (HAS)]. Revue des Maladies Respiratoires 2016	Paper about reimbursement, not focused on the role of CPGs
20	Autio LA et al. Measuring quality of care for essential hypertension. Holistic Nursing Practice 2001	Paper on QI/QA or quality indicators, not focused on the role of CPGs
21	Baji P et al. Comparative analysis of decision maker preferences for equity/efficiency attributes in reimbursement decisions in three European countries. European Journal of Health Economics 2016	Paper about reimbursement, not focused on the role of CPGs
22	Baker R.. Reforming primary care in England--again. Plans for improving the quality of care. Scandinavian Journal of Primary Health Care 2000	Paper on QI/QA or quality indicators, not focused on the role of CPGs
23	Balas EA et al. An expert system for performance-based direct delivery of published clinical evidence. Journal of the American Medical Informatics Association : JAMIA 1996	Paper about Performance measurement, not focused on CPGs
24	Barnsley J et al. Identifying performance indicators for family practice: assessing levels of consensus. Canadian Family Physician 2005	Paper about Performance measurement, not focused on CPGs

25	Barry P.. Perspectives on private practice. Professional malpractice insurance and practicing within professional guidelines. Perspectives in Psychiatric Care 2006	Paper about judicial/malpractice issues, not focused on the role of CPGs
26	Becker M et al. Guideline-based quality indicators-a systematic comparison of German and international clinical practice guidelines: protocol for a systematic review. Systematic Reviews 2018	Protocol
27	Bekkering GE et al. Development and Validation of Quality Indicators on Continuing Care for Patients With AUD: A Delphi Study. Alcohol & Alcoholism 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
28	Beletsi A et al. Comparing Use of Health Technology Assessment in Pharmaceutical Policy among Earlier and More Recent Adopters in the European Union. Value in Health Regional Issues 2018	Not related to CPGs or any of the roles
29	Belfroid E et al. Selection of key recommendations for quality indicators describing good quality outbreak response. BMC Infectious Diseases 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
30	Bell CM et al. Methodological issues in the use of guidelines and audit to improve clinical effectiveness in breast cancer in one United Kingdom health region. European Journal of Surgical Oncology 2000	Paper about implementation of CPGs (in general or specific cases), not focused on roles
31	Belleudi V et al. Neonatal outcomes following new reimbursement limitations on palivizumab in Italy. Archives of Disease in Childhood 2018	Paper about reimbursement, not focused on the role of CPGs
32	Bellmunt S et al. Healthcare quality indicators of peripheral artery disease based on systematic reviews. European Journal of Vascular & Endovascular Surgery 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
33	Bennett N et al. Hidden curriculum in continuing medical education. Journal of Continuing Education in the Health Professions 2004	Paper about education, not focused on CPGs
34	Berlowitz DR et al. Quality improvement implementation in the nursing home. Health Services Research 2003	Paper on QI/QA or quality indicators, not focused on the role of CPGs
35	Bermudez-Tamayo C et al. Evaluation of quality improvement for cesarean sections caesarean section programmes through mixed methods.[Erratum appears in Implement Sci. 2016;11(1):37; PMID: 26984271]. Implementation Science 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
36	Berthiaume JT et al. Aligning financial incentives with "get with the guidelines" to improve cardiovascular care. American Journal of Managed Care 2004	Paper about implementation of CPGs (in general or specific cases), not focused on roles

37	Birchall MA.. Guidelines, standards and protocols in head and neck cancer: tools not restraints. Clinical Otolaryngology & Allied Sciences 1999	Paper about CPGs in general or about specific topics, not focused on our roles of interest
38	Blot SI et al. Evidence-based guidelines for the prevention of ventilator-associated pneumonia: Results of a knowledge test among intensive care nurses. Intensive Care Medicine 2007	Paper with CPGs recommendations
39	Boesten J et al. Defining antimicrobial prescribing quality indicators: what is a new prescription?. European Journal of Clinical Pharmacology 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
40	Boivin JM. et al. [Official recommendations and guidelines for the management and reimbursement of severe hypertension as a chronic disease]. Presse Medicale 2009	Paper about reimbursement, not focused on the role of CPGs
41	Bollini P et al. Guidelines-based indicators to measure quality of antenatal care. Journal of Evaluation in Clinical Practice 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
42	Bonfill X et al. Development of quality of care indicators from systematic reviews: the case of hospital delivery. Implementation Science 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
43	Bonney A et al. Will the NHHRC recommendations drive quality performance?. Australian Family Physician 2009	Paper on QI/QA or quality indicators, not focused on the role of CPGs
44	Bonow RO et al. ACCF/AHA methodology for the development of quality measures for cardiovascular technology: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures. Circulation 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
45	Bonte AS et al. Quality indicators for the management of endometrial, cervical and ovarian cancer. European Journal of Surgical Oncology. 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
46	Borenstein J et al. The association between quality improvement activities performed by managed care organizations and quality of care. American Journal of Medicine 2004	Paper on QI/QA or quality indicators, not focused on the role of CPGs
47	Borisenko O et al. Clinical Indications, Utilization, and Funding of Bariatric Surgery in Europe. Obesity Surgery 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
48	Breugom AJ et al. Quality assurance in the treatment of colorectal cancer: the EURECCA initiative. Annals of Oncology 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
49	Briffa TG et al. Should fee-for-service be for all guideline-advocated acute coronary syndrome (ACS) care? Observations from the Snapshot ACS study. Australian Health Review 2015	Paper about reimbursement, not focused on the role of CPGs

50	Brook RH.. Practice guidelines: to be or not to be. Lancet 1996	Paper about CPGs in general or about specific topics, not focused on our roles of interest
51	Bruggemann S et al. Practice guidelines in rehabilitation: Infringement upon physicians' autonomy or foundation for better outcomes?. [German]. Rehabilitation 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest
52	Burda A et al. Recommended vs reimbursed vs actually used chemiotherapeutics in pancreatic adenocarcinoma in Poland. Value in Health 2016	Paper about reimbursement, not focused on the role of CPGs
53	Burge FI et al. Quality indicators for cardiovascular primary care. Canadian Journal of Cardiology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
54	Busch AB et al. Quality of care in a Medicaid population with bipolar I disorder. Psychiatric Services 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
55	Butler WM et al. Clinical practice and quality assurance challenges in modern brachytherapy sources and dosimetry. International Journal of Radiation Oncology, Biology, Physics 2008	Not related to CPGs or any of the roles
56	Chartrand M et al. Development of Quality Indicators to Assess Oral Anticoagulant Management in Community Pharmacies for Patients with Atrial Fibrillation. Journal of Managed Care & Specialty Pharmacy 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
57	Chen WH et al. The medicolegal issue of tissue plasminogen activator in ischemic stroke: a review of judiciary decrees in Taiwan. Acta Neurologica Taiwanica 2011	Paper about judicial/malpractice issues, not focused on the role of CPGs
58	Chin MH et al. Quality of diabetes care in community health centers. American Journal of Public Health 2000	Paper on QI/QA or quality indicators, not focused on the role of CPGs
59	Chin-Lenn L et al. Quality indicators for ductal carcinoma in situ (DCIS) of the breast: development using a multidisciplinary delphi process and its use in monitoring population-based treatment. Journal of Surgical Oncology 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
60	Christian CS et al. Measuring Quality Gaps in TB Screening in South Africa Using Standardised Patient Analysis. International Journal of Environmental Research & Public Health [Electronic Resource] 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
61	Colebatch-Bourn AN et al. Are guidelines good value for money?. Rheumatology 2015	Paper about CPGs in general or about specific topics, not focused on our roles of interest
62	Cottrell J et al. Quality indicators for the diagnosis and management of chronic rhinosinusitis. International Forum of Allergy and Rhinology 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
63	Cretin S et al. Evaluating an integrated approach to clinical quality improvement: clinical	Paper on QI/QA or quality indicators, not focused on the role of CPGs

	guidelines, quality measurement, and supportive system design. Medical Care 2001	
64	Crosby E.. Review article: the role of practice guidelines and evidence-based medicine in perioperative patient safety. Canadian Journal of Anaesthesia 2013	Paper about CPGs in general or about specific topics, not focused on our roles of interest
65	Curtiss FR.. Chasing quality--clinical practice guidelines and HEDIS measures of asthma and depression therapy management. Journal of Managed Care Pharmacy 2006	Paper about CPGs in general or about specific topics, not focused on our roles of interest
66	Davies J.. Clinical guidelines as a tool for legal liability. An international perspective. Medicine & Law 2009	Paper about judicial/malpractice issues, not focused on the role of CPGs
67	Day S et al. Retinopathy of prematurity malpractice claims: the Ophthalmic Mutual Insurance Company experience. Archives of Ophthalmology 2009	Paper about judicial/malpractice issues, not focused on the role of CPGs
68	de Barros e Silva PGM et al. Improvement in quality indicators using NCDR registries: First international experience. International Journal of Cardiology 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
69	de Noronha JC et al. Quality improvement initiatives in Brazil: a progress report. Joint Commission Journal on Quality Improvement 1999	Paper on QI/QA or quality indicators, not focused on the role of CPGs
70	Dechartres A et al. Better prioritization to increase research value and decrease waste. BMC Medicine 2015	Paper on research prioritization (general or topic-specific), not focused on the role of CPGs
71	Demirci D et al. Do Turkish reimbursement recommendations cover current European Lipid Guidelines? A retrospective analysis of patients presenting with first acute coronary syndrom. [Turkish]. Turk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir 2017	Paper about reimbursement, not focused on the role of CPGs
72	Den Breejen EME et al. Development of guideline-based indicators for patient-centredness in fertility care: What patients add. Human Reproduction 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
73	Diamond LH.. Local implementation of clinical practice guidelines and continuous quality improvement: challenges and opportunities. Seminars in Dialysis 2000	Paper about implementation of CPGs (in general or specific cases), not focused on roles
74	Dick WF.. Setting standards and implementing quality improvement in trauma care. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 1996	Paper on QI/QA or quality indicators, not focused on the role of CPGs
75	Dijkstra R et al. The relationship between organisational characteristics and the effects of clinical guidelines on medical performance in	Paper about implementation of CPGs (in general or specific cases), not focused on roles

	hospitals, a meta-analysis. BMC Health Services Research 2006	
76	Dobesh PP et al. Role of the pharmacist in achieving performance measures to improve the prevention and treatment of venous thromboembolism. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 2013	Paper about Performance/Quality measurement, not focused on the role of CPGs
77	Donot PE.. [JACIE: from guidelines to clinical practice and continuous quality improvement, the Leon-Berard cancer center experience]. Bulletin du Cancer 2009	Paper on QI/QA or quality indicators, not focused on the role of CPGs
78	Doyle AJ et al. A review of the recommendations governing quality assurance of ultrasound systems used for guidance in prostate brachytherapy. Physica Medica 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
79	Dreesen M et al. Quality of care for cancer patients on home parenteral nutrition: development of key interventions and outcome indicators using a two-round Delphi approach. Supportive Care in Cancer 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
80	du Bois A et al. Impact of treatment guidelines and implementation of a quality assurance program on quality of care in endometrial cancer. Onkologie 2009	Paper about implementation of CPGs (in general or specific cases), not focused on roles
81	Duffy FF et al. Quality of care measures for the treatment of bipolar disorder. Psychiatric Quarterly 2005	Paper about Performance/Quality measurement, not focused on the role of CPGs
82	Eagle KA et al. Closing the gap between science and practice: the need for professional leadership. Health Affairs 2003	Paper about implementation of CPGs (in general or specific cases), not focused on roles
83	Edge J et al. Inpatient care for children with diabetes: are standards being met?. Archives of Disease in Childhood 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
84	Ellis B et al. Standards for change: Developing international minimum standards for the care of older people in the emergency department. Canadian Journal of Emergency Medicine 2018	Paper about Performance/Quality measurement, not focused on the role of CPGs
85	Ellis SD et al. Are small reimbursement changes enough to change cancer care? reimbursement variation in prostate cancer treatment. Journal of Oncology Practice 2016	Paper about reimbursement, not focused on the role of CPGs
86	Ennis CS.. Physicians' role in clinical practice guidelines. Postgraduate Medicine 1996	Paper about CPGs in general or about specific topics, not focused on our roles of interest
87	Erhardt L et al. Quality assurance of secondary prevention--a solution to better implementation of guidelines. Scandinavian Cardiovascular Journal 1999	Paper about implementation of CPGs (in general or specific cases), not focused on roles
88	Escribano-Ferrer B et al. Quality of Health Care in Ghana: Mapping of Interventions and the Way Forward. Ghana Medical Journal 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs

89	Ewald DA et al. Development of a core set of quality indicators for paediatric primary care practices in Europe, COSI-PPC-EU. European Journal of Pediatrics 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
90	Fairfield G et al. Implications of managed care for health systems, clinicians, and patients. BMJ 1997	Not related to CPGs or any of the roles
91	Fantini G et al. Quality of care indicators for schizophrenia: determinants of observed variations among Italian Departments of Mental Health. Results from the ETAS DSM study. Epidemiology & Psychiatric Science 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
92	Fasola G et al. Adopting integrated care pathways in non-small-cell lung cancer: from theory to practice. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2012	Not related to CPGs or any of the roles
93	Fein IA et al. Clinical practice guidelines: culture eats strategy for breakfast, lunch, and dinner. Critical Care Medicine 2008	Paper about CPGs in general or about specific topics, not focused on our roles of interest
94	Ferguson B et al. Malpractice in Emergency Medicine-A Review of Risk and Mitigation Practices for the Emergency Medicine Provider. Journal of Emergency Medicine 2018	Paper about judicial/malpractice issues, not focused on the role of CPGs
95	Figueiredo TA et al. Evidence-based process for decision-making in the analysis of legal demands for medicines in Brazil. Cadernos de Saude Publica 2013	Paper about Performance/Quality measurement, not focused on the role of CPGs
96	Folger SJ et al. Evidence-based guidance on Selected Practice Recommendations for Contraceptive Use: identification of research gaps. Contraception 2013	Paper on research prioritization (general or topic-specific), not focused on the role of CPGs
97	Fonarow GC.. Improving quality of care and outcomes for heart failure: Role of registries. Circulation Journal 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
98	Francis DO.. Bench to trench: how evidence and guidelines shape health care policy and practice. Otolaryngology - Head & Neck Surgery 2013	Paper about CPGs in general or about specific topics, not focused on our roles of interest
99	Freeman JL et al. Measuring the performance of screening mammography in community practice with Medicare claims data. Women & Health 2003	Paper about Performance/Quality measurement, not focused on the role of CPGs
100	Frenzel JC et al. Ongoing provision of individual clinician performance data improves practice behavior. Anesthesia & Analgesia 2010	Paper about Performance/Quality measurement, not focused on the role of CPGs
101	Fukuda H et al. Change in clinical practice after publication of guidelines on breast cancer treatment. International Journal for Quality in Health Care 2009	Paper about CPGs in general or about specific topics, not focused on our roles of interest

102	Gaebel W et al. [DGPPN policy paper on quality assurance and guidelines. Current status and perspectives of guideline development]. Nervenarzt 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
103	Ganju V.. Mental health quality and accountability: the role of evidence-based practices and performance measurement. Administration & Policy in Mental Health 2006	Paper about Performance/Quality measurement, not focused on the role of CPGs
104	Garnick DW et al. Performance measures for alcohol and other drug services. Alcohol Research & Health: the Journal of the National Institute on Alcohol Abuse & Alcoholism 2006	Paper about Performance/Quality measurement, not focused on the role of CPGs
105	Garson Jr A.. U.S. Healthcare: The Intertwined Caduceus of Physicians, Coverage, Quality, and Cost. Journal of the American College of Cardiology 2004	Paper about reimbursement, not focused on the role of CPGs
106	Germansky KA et al. Development of quality measures for monitoring and improving care in gastroenterology. Best Practice and Research: Clinical Gastroenterology 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
107	Ghali JK et al. Guidelines, performance measures, and the practice of medicine: mind the gap. Journal of Cardiac Failure 2010	Duplicate of an included paper (Ghali 2010)
108	Giesen P et al. Out-of-hours primary care: development of indicators for prescribing and referring. International Journal for Quality in Health Care 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
109	Gifford F.. Outcomes research and practice guidelines. Upstream issues for downstream users. Hastings Center Report 1996	Paper about CPGs in general or about specific topics, not focused on our roles of interest
110	Gilbert L et al. Aligning hospital and physician performance incentives: a shared success model. Joint Commission Journal on Quality & Patient Safety 2008	Paper about Performance incentives, not focused on CPGs
111	Gill PJ et al. Primary care quality indicators for children: measuring quality in UK general practice. British Journal of General Practice 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
112	Glickman SW et al. Pay for performance, quality of care, and outcomes in acute myocardial infarction. JAMA 2007	Paper about Performance incentives, not focused on CPGs
113	Goebel RH et al. Clinical practice guidelines for pressure ulcer prevention can prevent malpractice lawsuits in older patients. Journal of Wound, Ostomy, & Continence Nursing 1999	Paper about judicial/malpractice issues, not focused on the role of CPGs
114	Goldsmith M et al. The role of community oncologists in the prevention and treatment of VTE: clinical guidelines and CMS payment policy. Community Oncology 2009	Paper about reimbursement, not focused on the role of CPGs

115	Gray MP et al. Improving Guideline-Based Care of Acute Asthma in a Pediatric Emergency Department. Pediatrics 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
116	Grifoni P et al. A system for the description of healthcare guidelines. Studies in Health Technology & Informatics 1999	Paper about CPGs in general or about specific topics, not focused on our roles of interest
117	Grimshaw JM et al. Disseminating and implementing guidelines: article 13 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society 2012	Paper about implementation of CPGs (in general or specific cases), not focused on roles
118	Groce JB.. Translating evidence-based guidelines into performance measures for venous thromboembolism and acute coronary syndrome. American Journal of Health-System Pharmacy 2007	Paper about Performance/Quality measurement, not focused on the role of CPGs
119	Grunebaum A.. Error Reduction and Quality Assurance in Obstetrics. Clinics in Perinatology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
120	Guiberteau MJ et al. Practice guidelines: the radiology perspective. Journal of the American College of Radiology 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest
121	Guru V et al. The identification and development of Canadian coronary artery bypass graft surgery quality indicators. Journal of Thoracic and Cardiovascular Surgery 2005	Paper on QI/QA or quality indicators, not focused on the role of CPGs
122	Haas C et al. Assessment of quality performance measures for primary percutaneous coronary intervention: A report from a tertiary referral centre in Switzerland. European Heart Journal Acute Cardiovascular Care 2016	Paper about Performance/Quality measurement, not focused on the role of CPGs
123	Haase R et al. Improving diabetes care and outcomes in a rural primary care clinic. Joint Commission Journal on Quality & Patient Safety 2006	Paper on QI/QA or quality indicators, not focused on the role of CPGs
124	Haines ST.. Improving the quality of care for patients at risk for venous thromboembolism. American Journal of Health-System Pharmacy 2010	Paper on QI/QA or quality indicators, not focused on the role of CPGs
125	Haitsma G et al. Access to anti-cancer drugs in India: is there a need to revise reimbursement policies?. Expert Review of Pharmacoeconomics and Outcomes Research 2018	Paper about reimbursement, not focused on the role of CPGs
126	Halfon N et al. Improving the quality of healthcare for children: implementing the results of the AHSR research agenda conference. Health Services Research 1998	Paper on QI/QA or quality indicators, not focused on the role of CPGs

127	Hargraves JL et al. Practice characteristics and performance of primary care practitioners. Medical Care 1996	Paper about Performance/Quality measurement, not focused on the role of CPGs
128	Harlin SL et al. Chronic wounds of the lower extremity: a preliminary performance measurement set. Plastic & Reconstructive Surgery 2008	Paper about Performance/Quality measurement, not focused on the role of CPGs
129	Harolds JA.. Quality and Safety in Health Care, Part XXXIV: The PINNACLE Registry. Clinical Nuclear Medicine 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
130	Harr DS et al. Developing quality indicators as educational tools to measure the implementation of clinical practice guidelines. American Journal of Medical Quality 1996	Paper on QI/QA or quality indicators, not focused on the role of CPGs
131	Hartig JR et al. Physician performance improvement: an overview of methodologies. Clinical & Experimental Rheumatology 2007	Paper about Performance/Quality measurement, not focused on the role of CPGs
132	Hastings K.. A view from the Agency for Health Care Policy and Research: the use of language in clinical practice guidelines. Joint Commission Journal on Quality Improvement 1993	Paper about CPGs in general or about specific topics, not focused on our roles of interest
133	Hauck K et al. Reducing avoidable inequalities in health: a new criterion for setting health care capitation payments. Health Economics 2002	Paper about reimbursement, not focused on the role of CPGs
134	Hayes S.. Reviewing and improving a clinical effectiveness department's quality assurance model: lessons learned. International Journal of Health Care Quality Assurance 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
135	Heaney D.. Clinical guidelines may obviate need for thought. BMJ 1996	Paper about CPGs in general or about specific topics, not focused on our roles of interest
136	Heidenreich PA et al. Impact of an Expanded Hospital Recognition Program for Stroke Quality of Care. Journal of the American Heart Association 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
137	Hendriks HJM et al. Development and implementation of national practice guidelines: a prospect for continuous quality improvement in physiotherapy. Physiotherapy 2000	Paper about implementation of CPGs (in general or specific cases), not focused on roles
138	Herberger K et al. Development and use of guideline-derived quality indicators for community lymphoedema. Journal of the European Academy of Dermatology & Venereology 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
139	Hermanides HS et al. Development of quality indicators for the antibiotic treatment of complicated urinary tract infections: A first step to measure and improve care. Clinical Infectious Diseases 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
140	Hermann RC et al. Aligning measurement-based quality improvement with implementation of	Not related to CPGs or any of the roles

	evidence-based practices. Administration & Policy in Mental Health 2006	
141	Hermens RP et al. Development of quality indicators for diagnosis and treatment of patients with non-small cell lung cancer: a first step toward implementing a multidisciplinary, evidence-based guideline. Lung Cancer 2006	Paper on QI/QA or quality indicators, not focused on the role of CPGs
142	Hewitt-Taylor J.. Clinical guidelines and care protocols. Intensive & Critical Care Nursing 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest
143	Heyes AE et al. Hta and Reimbursement Considerations for Rare Diseases in European Markets: What Are the Implications for Manufacturers?S?. Value in Health 2018	Paper about reimbursement, not focused on the role of CPGs
144	Hollingsworth J.. Developing and Implementing a Quality Assurance Strategy for Electroconvulsive Therapy. Developing & Implementing a Quality Assurance Strategy for Electroconvulsive Therapy 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
145	Hur JW et al. Rheumatoid arthritis patients fulfilling Korean National Health Insurance reimbursement guidelines for anti-tumor necrosis factor-alpha treatment and comparison to other guidelines. Rheumatology International 2015	Paper about reimbursement, not focused on the role of CPGs
146	Jacob S et al. Estimation of an optimal chemotherapy utilisation rate for colon cancer: an evidence-based benchmark for cancer care. European Journal of Cancer 2009	Paper about Performance/Quality measurement, not focused on the role of CPGs
147	Jaeger KA.. Do we need new guidelines?. Ultraschall in der Medizin 2008	Paper about CPGs in general or about specific topics, not focused on our roles of interest
148	Jansen MJ et al. Quality indicators indicate good adherence to the clinical practice guideline on "Osteoarthritis of the hip and knee" and few prognostic factors influence outcome indicators: a prospective cohort study. European journal of physical & rehabilitation medicine. 2010	Paper about implementation of CPGs (in general or specific cases), not focused on roles
149	Jerrold L.. Litigation, legislation, and ethics. Errors of judgement and the standard of care. American Journal of Orthodontics & Dentofacial Orthopedics 1997	Paper about judicial/malpractice issues, not focused on the role of CPGs
150	Jerrold L.. Litigation, legislation, and ethics. Determining a national standard of care. American Journal of Orthodontics & Dentofacial Orthopedics 2004	Paper about judicial/malpractice issues, not focused on the role of CPGs
151	Jerrold L.. Litigation, legislation, and ethics. Models and the standard of care. American Journal of Orthodontics & Dentofacial Orthopedics 2006	Paper about judicial/malpractice issues, not focused on the role of CPGs
152	Johnstone J et al. Guidelines and quality measures: do they improve outcomes of patients	Paper on QI/QA or quality indicators, not focused on the role of CPGs

	with community-acquired pneumonia?. Infectious Disease Clinics of North America 2013	
153	Jolin J et al. Using an Inpatient Quality Improvement Curriculum for Internal Medicine Residents to Improve Pneumococcal Conjugate Vaccine Administration Rates. Joint Commission Journal on Quality and Patient Safety 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
154	Kamel M et al. Reimbursements and frequency of tests in privately insured testicular cancer patients in the United States: Implications to national guidelines. Urology Annals 2017	Paper about reimbursement, not focused on the role of CPGs
155	Kampstra NA et al. Health outcomes measurement and organizational readiness support quality improvement: a systematic review. BMC health services research 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
156	Kittle K et al. Using a pediatric database to drive quality improvement. Seminars in Pediatric Surgery 2002	Paper on QI/QA or quality indicators, not focused on the role of CPGs
157	Kliger AS.. Clinical practice guidelines and performance measures in ESRD. American journal of kidney diseases : the official journal of the National Kidney Foundation 1998	Paper about Performance/Quality measurement, not focused on the role of CPGs
158	Knutson DJ.. The role of strategic alliances in ensuring health care quality: a health care system perspective. Clinical Therapeutics 1997	Paper on QI/QA or quality indicators, not focused on the role of CPGs
159	Ko DT et al. Canadian quality indicators for percutaneous coronary interventions. Canadian Journal of Cardiology 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
160	Kobberling J.. [Rationalization attempts: guidelines, evidence-based medicine]. Zeitschrift fur Arztliche Fortbildung und Qualitatssicherung 2000	Paper about CPGs in general or about specific topics, not focused on our roles of interest
161	Kohli H et al. NICE guidance in the Scottish context. Scottish Medical Journal 2009	Paper about CPGs in general or about specific topics, not focused on our roles of interest
162	Kolitsi Z et al. Quality assurance in conformal radiotherapy: DYNARAD consensus report on practice guidelines. Radiotherapy & Oncology 1997	Paper on QI/QA or quality indicators, not focused on the role of CPGs
163	Kornides ML et al. Content of web-based continuing medical education about HPV vaccination. Vaccine 2017	Paper about education, not focused on CPGs
164	Kurtin P.. Standardize to excellence: improving the quality and safety of care with clinical pathways. Pediatric Clinics of North America 2009	Paper on QI/QA or quality indicators, not focused on the role of CPGs
165	LaBresh KA et al. Improved treatment of hospitalized coronary artery disease patients with the get with the guidelines program. Critical Pathways in Cardiology 2007	Paper about implementation of CPGs (in general or specific cases), not focused on roles

166	LaBresh KA et al. Using "get with the guidelines" to improve cardiovascular secondary prevention. Joint Commission Journal on Quality & Safety 2003	Paper about implementation of CPGs (in general or specific cases), not focused on roles
167	Langer T et al. [The German Guideline Program in Oncology (GGPO): A central core of an evidence-based, patient-centered interdisciplinary oncology?]. Zeitschrift fur Evidenz Fortbildung und Qualitat im Gesundheitswesen 2015	Paper about CPGs in general or about specific topics, not focused on our roles of interest
168	Langiano T et al. Quality improvement measures adopted by the Italian National Health Service. International Journal of Artificial Organs 1998	Paper on QI/QA or quality indicators, not focused on the role of CPGs
169	Larkin A et al. Effect of an online continuing medical education and clinician coaching quality improvement initiative on antiplatelet medication adherence and hospital readmissions in patients with acute coronary syndrome. Journal of the American College of Cardiology 2017	Paper about education, not focused on CPGs
170	Larson E.. Status of practice guidelines in the United States: CDC guidelines as an example. Preventive Medicine 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
171	Lazorick S et al. Structured intervention utilizing state professional societies to foster quality improvement in practice. Journal of Continuing Education in the Health Professions 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
172	Lee AJ.. The role of financial incentives in shaping clinical practice patterns and practice efficiency. American Journal of Cardiology 1997	Paper about Performance incentives, not focused on CPGs
173	Lee TH et al. Clinical goals and performance measures for cholesterol management in secondary prevention of coronary heart disease. JAMA 2000	Paper about Performance/Quality measurement, not focused on the role of CPGs
174	Lenzer J.. Why we can't trust clinical guidelines. BMJ 2013	Paper about CPGs in general or about specific topics, not focused on our roles of interest
175	Lescoe-Long M et al. Defining the utility of clinically acceptable variations in evidence-based practice guidelines for evaluation of quality improvement activities. Evaluation & the Health Professions 1999	Paper on QI/QA or quality indicators, not focused on the role of CPGs
176	Lesho EP et al. Do clinical practice guidelines improve processes or outcomes in primary care?. Military Medicine 2005	Paper about CPGs in general or about specific topics, not focused on our roles of interest
177	Levin A.. Practice guidelines do improve patient outcomes: association or causation?. Blood Purification 2008	Paper about CPGs in general or about specific topics, not focused on our roles of interest
178	Lim HW et al. Research agenda consensus conference. Journal of the American Academy of Dermatology 2013	Paper on research prioritization (general or topic-specific), not focused on the role of CPGs

179	Lim SG et al. Reimbursement policies in the Asia-Pacific for chronic hepatitis B. Hepatology International 2015	Paper about reimbursement, not focused on the role of CPGs
180	Lin GA et al. Impact of changes in clinical practice guidelines on assessment of quality of care. Medical Care 2010	Paper about implementation of CPGs (in general or specific cases), not focused on roles
181	Lind S et al. Quality indicators for palliative and end of life care: a review of Swedish policy documents. BMJ supportive & palliative care 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
182	Lindenauer PK et al. The role of the institutional review board in quality improvement: a survey of quality officers, institutional review board chairs, and journal editors. American Journal of Medicine 2002	Paper on QI/QA or quality indicators, not focused on the role of CPGs
183	Litvin CB et al. Quality indicators for primary care: an example for chronic kidney disease. Journal of Ambulatory Care Management 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
184	Lohr KN.. The role of research in setting priorities for health care. Journal of Evaluation in Clinical Practice 1996	Paper on research prioritization (general or topic-specific), not focused on the role of CPGs
185	Long MJ.. Clinical practice guidelines: when the tool becomes the rule. Journal of Evaluation in Clinical Practice 2001	Paper about CPGs in general or about specific topics, not focused on our roles of interest
186	Lu CY et al. Insurance coverage policies for pharmacogenomic and multi-gene testing for cancer. Journal of Personalized Medicine 2018	Paper about reimbursement, not focused on the role of CPGs
187	Lundsberg LS et al. Quality assurance practices in obstetric care: A survey of hospitals in California. Obstetrics and Gynecology 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
188	Lynn B et al. Identifying Primary Care Physicians Continuing Education Needs by Examining Clinical Practices, Attitudes, and Barriers to Screening Across Multiple Cancers. Journal of cancer education: the official journal of the American Association for Cancer Education 2018	Paper about education, not focused on CPGs
189	Lyons TW et al. A QI Initiative to Reduce Hospitalization for Children With Isolated Skull Fractures. Pediatrics 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
190	Makdisse M et al. Effect of implementing an acute myocardial infarction guideline on quality indicators. Einstein 2013	Paper about implementation of CPGs (in general or specific cases), not focused on roles
191	Margo CE.. Quality care and practice variation: the roles of practice guidelines and public profiles. Survey of Ophthalmology 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest
192	Marshall AD et al. Restrictions for reimbursement of interferon-free direct-acting antiviral therapies for HCV infection in Europe. Journal of Hepatology 2017	Paper about reimbursement, not focused on the role of CPGs

193	Marshall JL et al. Implementation of a performance improvement initiative in colorectal cancer care. Journal of oncology practice/American Society of Clinical Oncology 2012	Paper about Performance/Quality measurement, not focused on the role of CPGs
194	Martinowsky M.. [Guidelines and quality improvement management]. Archives de Pediatrie 2008	Paper about CPGs in general or about specific topics, not focused on our roles of interest
195	Martirosyan L et al. Prescribing quality indicators of type 2 diabetes mellitus ambulatory care. Quality & Safety in Health Care 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
196	Mason J et al. A framework for incorporating cost-effectiveness in evidence-based clinical practice guidelines. Health Policy 1999	Paper about CPGs in general or about specific topics, not focused on our roles of interest
197	Mayeaux EJ et al. Systematic Review of International Colposcopy Quality Improvement Guidelines. Journal of Lower Genital Tract Disease 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
198	Mayeaux EJ et al. ASCCP Colposcopy Standards: Colposcopy Quality Improvement Recommendations for the United States. Journal of Lower Genital Tract Disease 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
199	Mazmanian PE et al. Continuing medical education effect on clinical outcomes: effectiveness of continuing medical education: American College of Chest Physicians Evidence-Based Educational Guidelines. Chest 2009	Paper about education, not focused on CPGs
200	Mazzone PJ et al. Quality indicators for the evaluation of patients with lung cancer. CHEST 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
201	McGory ML et al. Development of quality indicators for patients undergoing colorectal cancer surgery. Journal of the National Cancer Institute 2006	Paper on QI/QA or quality indicators, not focused on the role of CPGs
202	McIrvine AJ.. Guidelines are not directives. Hospital Medicine (London) 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
203	Melmed GY et al. Quality indicators for inflammatory bowel disease: development of process and outcome measures. Inflammatory Bowel Diseases 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
204	Melnyk BM.. Important information about clinical practice guidelines: key tools for improving quality of care and patient outcomes. Worldviews on Evidence-Based Nursing 2015	Paper about CPGs in general or about specific topics, not focused on our roles of interest
205	Miaskowski C et al. Interdisciplinary guidelines for the management of acute pain: implications for quality improvement. Journal of Nursing Care Quality 1992	Paper on QI/QA or quality indicators, not focused on the role of CPGs

206	Mims JW.. Targeting Quality Improvement in Clinical Practice Guidelines. Otolaryngology-Head & Neck Surgery 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
207	Minkoff NB.. The role of guidelines in managing diseases. Managed Care 2006	Paper about CPGs in general or about specific topics, not focused on our roles of interest
208	Mishra S.. Western guidelines or practice algorithms?-Yorkshire Pudding or Dal Makhni!. Indian Heart Journal 2016	Paper about CPGs in general or about specific topics, not focused on our roles of interest
209	Mohanty KC.. Influence of guidelines in determining medical negligence. BMJ 2005	Paper about judicial/malpractice issues, not focused on the role of CPGs
210	Molena D et al. Does Quality of Care Matter? A Study of Adherence to National Comprehensive Cancer Network Guidelines for Patients with Locally Advanced Esophageal Cancer. Journal of Gastrointestinal Surgery 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
211	Montgomery JS et al. Quality indicators in the management of bladder cancer. Journal of the National Comprehensive Cancer Network 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
212	Mosadeghrad AM.. Healthcare service quality: towards a broad definition. International Journal of Health Care Quality Assurance 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
213	Mourad SM et al. Guideline-based development of quality indicators for subfertility care. Human Reproduction 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
214	Mourad SM et al. Variation in subfertility care measured by guideline-based performance indicators. Human Reproduction 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
215	Musunuru K.. Do Evidence-Based Clinical Guidelines Do More Harm Than Good?. Cardiac Cath Lab Director 2011	Paper about CPGs in general or about specific topics, not focused on our roles of interest
216	Nasic M et al. Internal quality audit and quality standards as a method of quality improvement at the Department of Ophthalmology, University Hospital. Collegium Antropologicum 2005	Paper on QI/QA or quality indicators, not focused on the role of CPGs
217	Natsch S et al. The role of clinical guidelines, policies and stewardship. Journal of Hospital Infection 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
218	Ncayiyana DJ.. Clinical guidelines--are they of any use?. South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest
219	Nguyen-Ha PT et al. A Quality Assessment of a Collaborative Model of a Pediatric Antimicrobial Stewardship Program. Pediatrics 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
220	Nuckols T et al. Quality measures for the diagnosis and non-operative management of carpal tunnel syndrome in occupational settings. Journal of Occupational Rehabilitation 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
221	O'Connor PJ.. Adding value to evidence-based clinical guidelines. JAMA 2005	Paper about CPGs in general or about specific topics, not focused on our roles of interest

222	Ohtera S et al. Proposal of quality indicators for cardiac rehabilitation after acute coronary syndrome in Japan: a modified Delphi method and practice test. BMJ Open 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
223	Ollenschlager G et al. [The National Programme for Disease Management Guidelines. Goals, contents, patient involvement]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2007	Paper about CPGs in general or about specific topics, not focused on our roles of interest
224	Oostendorp RA et al. Guideline-based development and practice test of quality indicators for physiotherapy care in patients with neck pain. Journal of Evaluation in Clinical Practice 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
225	Orentlicher D.. Practice guidelines: a limited role in resolving rationing decisions. Journal of the American Geriatrics Society 1998	Paper about CPGs in general or about specific topics, not focused on our roles of interest
226	Ouwens M et al. Development of indicators for patient-centred cancer care. Supportive Care in Cancer 2010	Paper on QI/QA or quality indicators, not focused on the role of CPGs
227	Owen RR et al. Using an explicit guideline-based criterion and implicit review to assess antipsychotic dosing performance for schizophrenia. International Journal for Quality in Health Care 2002	Paper about judicial/malpractice issues, not focused on the role of CPGs
228	Pacione T et al. Quality chemical dependency treatment in an era of cost containment: clinical guidelines for practitioners. Health & Social Work 1994	Paper about CPGs in general or about specific topics, not focused on our roles of interest
229	Paciorkowski N et al. Development of performance tracking for a pediatric hospitalist division. Hospital Pediatrics 2013	Paper about Performance/Quality measurement, not focused on the role of CPGs
230	Paeger A.. Quality improvement in Germany. Joint Commission Journal on Quality Improvement 1997	Paper on QI/QA or quality indicators, not focused on the role of CPGs
231	Palmer RH et al. What makes quality assurance effective? Results from a randomized, controlled trial in 16 primary care group practices. Medical Care 1996	Paper on QI/QA or quality indicators, not focused on the role of CPGs
232	Pantilat SZ et al. Effect of incentives on the use of indicated services in managed care. Western Journal of Medicine 1999	Paper about Performance incentives, not focused on CPGs
233	Papanicolas I et al. Do financial incentives trump clinical guidance? Hip Replacement in England and Scotland. Journal of Health Economics 2015	Paper about Performance incentives, not focused on CPGs
234	Pasztelyi Z et al. Practice guidelines in pediatric hematooncology: implementation and survey. A possible way for medical quality assurance. Pediatric Hematology & Oncology 2000	Paper about implementation of CPGs (in general or specific cases), not focused on roles

235	Petch MC.. Heart disease, guidelines, regulations, and the law. Heart 2002	Paper about CPGs in general or about specific topics, not focused on our roles of interest
236	Peter WF et al. Quality indicators for physiotherapy care in hip and knee osteoarthritis: development and clinimetric properties. Musculoskeletal Care 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
237	Petignat PA.. [Are the guidelines the standards we have to follow]. Revue Medicale Suisse 2009	Paper about CPGs in general or about specific topics, not focused on our roles of interest
238	Pierce EC.. The development of anesthesia guidelines and standards. Qrb. Quality Review Bulletin 1990	Paper about CPGs in general or about specific topics, not focused on our roles of interest
239	Pitts D.. Healthcare policy and urologic practice. Current Opinion in Urology 2017	Not related to CPGs or any of the roles
240	Purvis T et al. Systematic review of process indicators: including early rehabilitation interventions used to measure quality of acute stroke care. International Journal of Stroke 2009	Paper on QI/QA or quality indicators, not focused on the role of CPGs
241	Radford MJ et al. ACC/AHA 2007 methodology for the development of clinical data standards: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. Journal of the American College of Cardiology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
242	Ramirez-Barba EJ et al. Quality control in gastrointestinal surgery. Cirugia y Cirujanos 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
243	Ramsdale E.. Evidence-based guidelines and quality measures in the care of older adults. The Virtual Mentor 2013	Paper about CPGs in general or about specific topics, not focused on our roles of interest
244	Reeves MJ et al. Are quality improvements in the get with the guidelines: stroke program related to better care or better data documentation?. Circulation. Cardiovascular Quality & Outcomes 2011	Paper about implementation of CPGs (in general or specific cases), not focused on roles
245	Reisner A et al. Quality Improvement in Concussion Care: Influence of Guideline-Based Education. Journal of Pediatrics 2017	Paper about implementation of CPGs (in general or specific cases), not focused on roles
246	Riskin L et al. Quality assessment by external bodies: intended and unintended impact on healthcare delivery. Current Opinion in Anaesthesiology 2009	Not related to CPGs or any of the roles
247	Robertson D et al. U.S. payers' views on expansion of patient access to diseasemodifying therapies (DMTs) for multiple sclerosis. Multiple Sclerosis Journal 2017	Not related to CPGs or any of the roles
248	Rothe U et al. Evaluation of a diabetes management system based on practice guidelines, integrated care, and continuous quality management in a federal state of germany. Diabetes Care 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs

249	Rushforth B et al. Developing 'high impact' guideline-based quality indicators for UK primary care: a multi-stage consensus process. BMC Family Practice 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
250	Saag KG et al. Measuring quality in arthritis care: the Arthritis Foundation's quality indicator set for analgesics. Arthritis & Rheumatism 2004	Paper on QI/QA or quality indicators, not focused on the role of CPGs
251	Sadeghi-Demneh E et al. The influence of standards and clinical guidelines on prosthetic and orthotic service quality: a scoping review. Disability & Rehabilitation 2018	Paper about CPGs in general or about specific topics, not focused on our roles of interest
252	Sampsel SL et al. Methods to develop arthritis and osteoporosis measures: A view from the National Committee for Quality Assurance (NCQA). Clinical and Experimental Rheumatology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
253	Sanders JO.. Quality, Safety, and Value: The Current AAOS Initiatives. Journal of Pediatric Orthopedics 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
254	Sanders RC.. Legal problems related to obstetrical ultrasound. Annals of the New York Academy of Sciences 1998	Paper about judicial/malpractice issues, not focused on the role of CPGs
255	Santana MJ et al. Measuring patient-centred system performance: A scoping review of patient-centred care quality indicators. BMJ Open 2019	Paper about Performance/Quality measurement, not focused on the role of CPGs
256	Saturno PJ et al. Development and pilot test of a new set of good practice indicators for chronic cancer pain management. European Journal of Pain 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
257	Schriefer J et al. Patient safety and quality improvement: an overview of QI. Pediatrics in Review 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
258	Schulpen TW et al. Quality improvement of paediatric care in the Netherlands. Archives of Disease in Childhood 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
259	Sheikh SZ et al. Perceptions of a Continuing Medical Education Activity to Increase Knowledge of Vaccination in Adults with Chronic Inflammatory Conditions Among Clinicians. Journal of Allergy and Clinical Immunology 2019	Paper about education, not focused on CPGs
260	Shen M et al. Indications and reimbursement of cardiac computed tomography angiography: History, present and future perspectives. Journal of Cardiovascular Computed Tomography 2008	Paper about reimbursement, not focused on the role of CPGs
261	Sherman SE et al. Performance improvement: improving recognition of depression in primary care: a study of evidence-based quality	Paper about Performance/Quality measurement, not focused on the role of CPGs

	improvement. Joint Commission Journal on Quality & Safety 2004	
262	Sigsbee B et al. Practice improvement requires more than guidelines and quality measures. Neurology 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
263	Simpson RJ-Jr et al. Performance assessment model for guideline-recommended pharmacotherapy in the secondary prevention of coronary artery disease and treatment of left ventricular dysfunction. American Journal of Cardiology 1997	Paper about Performance/Quality measurement, not focused on the role of CPGs
264	Sinsky CA et al. The impact of expressions of treatment efficacy and out-of-pocket expenses on patient and physician interest in osteoporosis treatment: implications for pay-for-performance programs. Journal of General Internal Medicine 2008	Not related to CPGs or any of the roles
265	Sisk JE.. How are health care organizations using clinical guidelines?. Health Affairs 1998	Paper about implementation of CPGs (in general or specific cases), not focused on roles
266	Smit M et al. Postpartum haemorrhage in midwifery care in the Netherlands: validation of quality indicators for midwifery guidelines. BMC Pregnancy & Childbirth 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
267	Smit M et al. The development of quality indicators for the prevention and management of postpartum haemorrhage in primary midwifery care in the Netherlands. BMC Pregnancy & Childbirth 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
268	Smit KL et al. Sinusitis Treatment Guideline Adherence in the E-Visit Setting: A Performance Improvement Project. Applied Clinical Informatics 2016	Paper about Performance/Quality measurement, not focused on the role of CPGs
269	So JP et al. The use of three strategies to improve quality of care at a national level. Clinical Orthopaedics & Related Research 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
270	Solberg LI et al. Using continuous quality improvement to increase preventive services in clinical practice--going beyond guidelines. Preventive Medicine 1996	Paper on QI/QA or quality indicators, not focused on the role of CPGs
271	Solberg LI et al. The three faces of performance measurement: improvement, accountability, and research. The Joint Commission journal on quality improvement 1997	Paper about Performance/Quality measurement, not focused on the role of CPGs
272	Spitz B et al. Evolution of evidence-based guidelines for home care: Wisconsin's experience. Home healthcare nurse 2007	Paper about CPGs in general or about specific topics, not focused on our roles of interest
273	Spollett G.. Promoting continuing education in diabetes management. Endocrine Practice 2006	Paper about education, not focused on CPGs
274	Stafinski T et al. Funding the unfundable: mechanisms for managing uncertainty in	Paper about reimbursement, not focused on the role of CPGs

	decisions on the introduction of new and innovative technologies into healthcare systems. Pharmacoeconomics 2010	
275	Stafinski T et al. Role of centralized review processes for making reimbursement decisions on new health technologies in Europe. ClinicoEconomics and Outcomes Research 2011	Paper about reimbursement, not focused on the role of CPGs
276	Stason WB.. Can clinical practice guidelines increase the effectiveness and cost-effectiveness of poststroke rehabilitation?. Topics in Stroke Rehabilitation 1997	Paper about CPGs in general or about specific topics, not focused on our roles of interest
277	Steinberg EP et al. Evidence based? Caveat emptor!. Health Affairs 2005	Not related to CPGs or any of the roles
278	Stelfox HT et al. Measuring quality of care: considering conceptual approaches to quality indicator development and evaluation. Journal of Clinical Epidemiology 2013	Paper on QI/QA or quality indicators, not focused on the role of CPGs
279	Stienen JJ et al. Development of quality indicators based on a multidisciplinary, evidence-based guideline on pediatric constipation. European Journal of Pediatrics 2011	Paper on QI/QA or quality indicators, not focused on the role of CPGs
280	Stordeur S et al. Developing and measuring a set of process and outcome indicators for breast cancer. Breast 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
281	Sun BJ et al. Quality measures in ventral hernia repair: a systematic review. Hernia 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
282	Sutter R.. Hospital Performance With Myocardial Reperfusion Therapy: Are Hospitals Capable of Meeting Established Guidelines?. Critical Pathways in Cardiology 2003	Paper about Performance/Quality measurement, not focused on the role of CPGs
283	Tafuri S et al. An audit about clinical governance skills in Italian medical managers. Annali di Igiene 2013	Not related to CPGs or any of the roles
284	Taler G.. Clinical practice guidelines: their purposes and uses. Journal of the American Geriatrics Society 1996	Paper about CPGs in general or about specific topics, not focused on our roles of interest
285	Thompson DR et al. Clinical guidelines: some considerations. European Journal of Cardiovascular Nursing 2008	Paper about CPGs in general or about specific topics, not focused on our roles of interest
286	Thonon F et al. Identifying potential indicators to measure the outcome of translational cancer research: a mixed methods approach. Health Research Policy & Systems 2015	Paper on QI/QA or quality indicators, not focused on the role of CPGs
287	Thorstenson A et al. Impact of quality indicators on adherence to National and European guidelines for renal cell carcinoma. Scandinavian Journal of Urology 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
288	Tillinghast SJ.. Can Western quality improvement methods transform the Russian	Not related to CPGs or any of the roles

	health care system?. Joint Commission Journal on Quality Improvement 1998	
289	Tingle J.. Evidence-based nursing and the law. Clinical guidelines: legal and clinical risk management issues. British Journal of Nursing 1997	Paper about judicial/malpractice issues, not focused on the role of CPGs
290	Tisnado DM et al. Financial incentives for quality in breast cancer care. American Journal of Managed Care 2008	Paper about Performance incentives, not focused on CPGs
291	Tobin M et al. Clinical practice guidelines: A tool to measure variance. Australasian Psychiatry 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
292	Tu JV et al. Indicators of quality of care for patients with acute myocardial infarction. CMAJ Canadian Medical Association Journal 2008	Paper on QI/QA or quality indicators, not focused on the role of CPGs
293	Tullo E et al. What should we be teaching medical students about dementia?. International Psychogeriatrics 2011	Paper about education, not focused on CPGs
294	Ueda K et al. Development of quality indicators for low-risk labor care provided by midwives using a RAND-modified Delphi method. BMC Pregnancy & Childbirth 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
295	Ullman M et al. Performance measurement in prostate cancer care: beyond report cards. Urology 1996	Paper about Performance/Quality measurement, not focused on the role of CPGs
296	Valentini G et al. Disease-specific quality indicators, guidelines and outcome measures in scleroderma. Clinical & Experimental Rheumatology 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
297	Valuck T et al. Improving Oncology Quality Measurement in Accountable Care: Filling Gaps with Cross-Cutting Measures. Journal of Managed Care & Specialty Pharmacy 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
298	Valuck T et al. Solutions for filling gaps in accountable care measure sets. American Journal of Managed Care 2015	Not related to CPGs or any of the roles
299	van den Boogaard E et al. Development of guideline-based quality indicators for recurrent miscarriage. Reproductive Biomedicine Online 2010	Paper on QI/QA or quality indicators, not focused on the role of CPGs
300	van den Bosch CM et al. Development of quality indicators for antimicrobial treatment in adults with sepsis. BMC Infectious Diseases 2014	Paper on QI/QA or quality indicators, not focused on the role of CPGs
301	van der Sanden WJ et al. Clinical practice guidelines in dentistry: opinions of dental practitioners on their contribution to the quality of dental care. Quality & Safety in Health Care 2003	Paper about CPGs in general or about specific topics, not focused on our roles of interest
302	van Driel ML et al. Effects of an evidence report and policies lifting reimbursement restrictions for	Paper about reimbursement, not focused on the role of CPGs

	acid suppressants: analysis of the Belgian national database. Pharmacoepidemiology & Drug Safety 2008	
303	Van Harrison R et al. Integrating education into primary care quality and cost improvement at an academic medical center. Journal of Continuing Education in the Health Professions 2006	Paper about education, not focused on CPGs
304	Versteeg MH et al. Factors associated with the impact of quality improvement collaboratives in mental healthcare: an exploratory study. Implementation Science 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
305	Vlassov VV.. Russian experience and perspectives of quality assurance in healthcare through standards of care. Health Policy and Technology 2016	Paper on QI/QA or quality indicators, not focused on the role of CPGs
306	Vlayen J et al. Quality indicators for testicular cancer: a population-based study. European Journal of Cancer 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
307	Vockley J et al. Development of clinical guidelines for inborn errors of metabolism: commentary. Molecular Genetics & Metabolism 2013	Paper about CPGs in general or about specific topics, not focused on our roles of interest
308	Voinea-Griffin A et al. Pay for performance: will dentistry follow?. BMC Oral Health 2010	Paper about Performance incentives, not focused on CPGs
309	Walter HJ.. The use of clinical practice guidelines to enhance the quality of care. Journal of the American Academy of Child and Adolescent Psychiatry 2017	Paper about CPGs in general or about specific topics, not focused on our roles of interest
310	Wang G et al. Eligibility criteria in private and public coverage policies for BRCA genetic testing and genetic counseling. Genetics in Medicine 2011	Paper about reimbursement, not focused on the role of CPGs
311	Washington DL et al. Development of Quality Indicators for the Care of Women with Abnormal Uterine Bleeding by Primary Care Providers in the Veterans Health Administration. Women's Health Issues. 2018	Paper on QI/QA or quality indicators, not focused on the role of CPGs
312	Weber K.. Challenges and opportunities in developing quality initiatives in orthopaedics. Journal of Pediatric Orthopedics 2012	Paper on QI/QA or quality indicators, not focused on the role of CPGs
313	Wens J et al. Quality indicators for type-2 diabetes care in practice guidelines: an example from six European countries. Primary care diabetes 2007	Paper on QI/QA or quality indicators, not focused on the role of CPGs
314	Wettermark B et al. Recent national and regional drug reforms in Sweden: Implications for pharmaceutical companies in Europe. PharmacoEconomics 2008	Not related to CPGs or any of the roles
315	Winkler MF.. Clinical indicators for nutrition support. Topics in Clinical Nutrition 1995	Paper on QI/QA or quality indicators, not focused on the role of CPGs

316	Wish JB.. Quality and accountability in the ESRD program. Advances in Renal Replacement Therapy 2001	Paper on QI/QA or quality indicators, not focused on the role of CPGs
317	Wish J et al. The cost of implementing the Dialysis Outcomes Quality Initiative Clinical Practice Guidelines. Advances in Renal Replacement Therapy 1999	Paper about CPGs in general or about specific topics, not focused on our roles of interest
318	Woodman OL et al. Teaching pharmacology to medical students in an integrated problem-based learning curriculum: An Australian perspective. Acta Pharmacologica Sinica 2004	Paper about education, not focused on CPGs
319	Woolf SH et al. Evidence-based medicine: Interpreting studies and setting policy. Hematology/Oncology Clinics of North America 2000	Not related to CPGs or any of the roles
320	Worrall A.. The service context for clinical guidelines: supporting guideline implementation by assuring and improving the quality of service in which clinicians work. International Review of Psychiatry 2011	Paper about CPGs in general or about specific topics, not focused on our roles of interest
321	Worth H.. Quality assurance in the management of asthma and COPD: What do national disease management guidelines achieve?. [German]. Pneumologe 2017	Paper on QI/QA or quality indicators, not focused on the role of CPGs
322	Wranik WD et al. Drug attributes associated with the selection of drugs for reimbursement: a pilot stated preferences experiment with Canadian stakeholders. Expert Review of Pharmacoeconomics and Outcomes Research 2019	Paper about reimbursement, not focused on the role of CPGs
323	Wright SW et al. Evidence-based emergency medicine. Creating a system to facilitate translation of evidence into standardized clinical practice: a preliminary report. Annals of Emergency Medicine 2008	Not related to CPGs or any of the roles
324	Xu Y et al. Getting (Along) With the Guidelines: Reconciling Patient Autonomy and Quality Improvement Through Shared Decision Making. Academic Medicine 2016	Paper about CPGs in general or about specific topics, not focused on our roles of interest
325	Yazdany J et al. A quality indicator set for systemic lupus erythematosus. Arthritis & Rheumatism: Arthritis Care & Research 2009	Paper on QI/QA or quality indicators, not focused on the role of CPGs
326	Youssouf S et al. Effect of a Quality Improvement Program to Improve Guideline Adherence and Attainment of Clinical Standards in Dialysis Care: Report of Outcomes in Year 1. Nephron 2017	Paper about implementation of CPGs (in general or specific cases), not focused on roles
327	Zimlichman E et al. Clinical guidelines as a tool for ensuring good clinical practice. Israel Medical Association Journal: Imaj 2004	Paper about CPGs in general or about specific topics, not focused on our roles of interest

Appendix 5. Included studies (N=220)

#	Reference	Language	Country	Type of paper	Roles addressed/commented
1	Advani A et al. A framework for evidence-adaptive quality assessment that unifies guideline-based and performance-indicator approaches. Proceedings / AMIA 2002	English	US	Research	Quality of Care, Economic decisions
2	Advani A et al. Developing quality indicators and auditing protocols from formal guideline models: knowledge representation and transformations. Proceedings / AMIA 2003	English	US	Research	Quality of Care
3	Akl E et al. Curricula for teaching the content of clinical practice guidelines to family medicine and internal medicine residents in the US: a survey study. Implementation Science 2009	English	US	Research	Medical education, certification and licensing
4	Anderson G et al. Medical technology assessment and practice guidelines: their day in court. American Journal of Public Health 1993	English	US	Non-research	Judicial Decisions
5	Anderson G et al. When courts review medical appropriateness. Medical Care 1998	English	US	Research	Judicial Decisions
6	Andrews EJ et al. A review of clinical guidelines. British journal of surgery. 2004 Aug;91(8):956-64.. British journal of surgery 2004	English	Ireland	Non-research	Judicial Decisions
7	Appelbaum PS. Practice guidelines in psychiatry and their implications for malpractice. Hospital & Community Psychiatry 1992	English	US	Non-research	Judicial Decisions
8	Avraham R. Clinical practice guidelines: the warped incentives in the U.S. healthcare system. American	English	US	Non-research	Judicial Decisions

	Journal of Law & Medicine 2011				
9	Ayres P. Clinical governance: setting the scene. Hospital Medicine (London) 1999	English	UK	Non-research	Quality of Care
10	Baillie N et al. NICE guidelines series and the role of indicators. Epidemiologia e Psichiatria Sociale 2008	English	UK	Non-research	Quality of Care
11	Baines P. NICE head injury guidelines: review of the Judicial Decisions mandate. Emergency Medicine Journal 2005	English	UK	Non-research	Judicial Decisions
12	Baker R et al. Development of review criteria: linking guidelines and assessment of quality. BMJ 1995	English	UK	Non-research	Quality of Care
13	Balas EA et al. How to structure clinical practice guidelines for continuous quality improvement?. Journal of Medical Systems 1994	English	US	Research	Quality of Care
14	Ball JR. Practice guidelines and their role in quality assurance and cost effectiveness. Quality Assurance in Health Care 1990	English	US	Non-research	Quality of Care, Economic decisions
15	Bannister E et al. Curricula for Teaching Clinical Practice Guidelines in US Psychiatry Residency and Child and Adolescent Fellowship Programs: A Survey Study. Acad Psychiatry 2014	English	US	Research	Medical education, certification and licensing
16	Battista RN et al. Clinical practice guidelines: between science and art. CMAJ Canadian Medical Association Journal 1993	English	Canada	Non-research	Quality of Care, Other Health Policy/services/ management decisions, Judicial Decisions
17	BennettB et al. The NICE process for developing quality standards and indicators. Zeitschrift fur Evidenz Fortbildung und Qualitat im Gesundheitswesen 2014	English	UK	Non-research	Quality of Care
18	Bergman DA. Evidence-based guidelines and critical	English	US	Non-research	Quality of Care

	pathways for quality improvement. Pediatrics 1999				
19	Berlin L. Standards, guidelines, and roses. American Journal of Roentgenology 2003	English	US	Non-research	Judicial Decisions
20	Bhatt M. The role of clinical guidelines in medical negligence litigation: has India made the shift?. Indian Journal of Medical Ethics 2009	English	India	Non-research	Judicial Decisions
21	Birkner BR. National quality of care activities in Germany. International Journal for Quality in Health Care 1998	English	Germany	Non-research	Quality of Care
22	Bjerrum L et al. Guidelines accompanied by changes in reimbursement rules. Effects on lipid-lowering drug prescribing. Scandinavian Journal of Primary Health Care 2001	English	Denmark	Research	Economic decisions
23	Blomberg M et al. Research gaps in the management and prevention of cutaneous squamous cell carcinoma in organ transplant recipients. British Journal of Dermatology 2017	English	US	Non-research	Research Prioritization
24	Blomkalns AL et al. Guideline implementation research: exploring the gap between evidence and practice in the CRUSADE Quality Improvement Initiative. Academic Emergency Medicine 2007	English	US	Non-research	Quality of Care
25	Blozik E et al. Simultaneous development of guidelines and quality indicators -- how do guideline groups act? A worldwide survey. International Journal of Health Care Quality Assurance 2012	English	Germany	Research	Quality of Care
26	Blozik E et al. Evidence-based indicators for the measurement of quality of primary care using health	English	Germany/ Switzerland	Research	Quality of Care, Economic decisions

	insurance claims data in Switzerland: results of a pragmatic consensus process. BMC Health Services Research 2018				
27	Bogdan-Lovis E et al. It's NOT FAIR! Or is it? The promise and the tyranny of evidence-based performance assessment. Theoretical Medicine & Bioethics 2012	English	US	Non-research	Quality of Care
28	Bogh SB et al. Accreditation and improvement in process quality of care: a nationwide study. International Journal for Quality in Health Care 2015	English	Denmark	Research	Quality of Care
29	Boscolo-Berto R. Judicial Decisions claims and bias in creating clinical practice guidelines: which step in which direction?. International Journal of Urology 2010	English	Italy	Non-research	Judicial Decisions
30	Bosnjak S. The importance of clinical practice guidelines (CPGs) for the quality and development of supportive care in Central and Eastern European (CEE) countries. Support Care Cancer 2003	English	Serbia	Non-research	Quality of Care
31	Bretthauer M et al. When no guideline recommendation is the best recommendation. Lancet 2018	English	Norway	Non-research	Research Prioritization
32	Browman GP et al. The role of guidelines in quality improvement for cancer surgery. Journal of Surgical Oncology 2009	English	Canada	Research	Quality of Care
33	Buffart LM et al. Evidence-based physical activity guidelines for cancer survivors: current guidelines, knowledge gaps and future research directions. Cancer Treatment Reviews 2014	English	Netherlands	Non-research	Research Prioritization
34	Cabana MD et al. The role of clinical practice guidelines in	English	UK	Non-research	Quality of Care

	enhancing quality and reducing racial/ethnic disparities in paediatrics. Paediatric Respiratory Reviews 2002				
35	Campbell SM et al. Research methods used in developing and applying quality indicators in primary care. Quality & Safety in Health Care 2002	English	UK	Non-research	Quality of Care
36	Carnett WG. Clinical practice guidelines: a tool to improve care. Quality Management in Health Care 1999	English	US	Non-research	Quality of Care
37	Chambers JD et al. Medicare is scrutinizing evidence more tightly for national Economic determinations. Health Affairs 2015	English	US	Research	Economic decisions
38	Chambers JD et al. Examining Evidence in U.S. Payer Economic Policies for Multi-Gene Panels and Sequencing Tests. International Journal of Technology Assessment in Health Care 2017	English	US	Research	Economic decisions
39	Chambers JD et al. Variation in Private Payer Economic of Rheumatoid Arthritis Drugs. Journal of Managed Care & Specialty Pharmacy 2016	English	US	Research	Economic decisions
40	Chambers JD et al. A Comparison of Economic Restrictions for Biopharmaceuticals and Medical Procedures. Value in Health 2018	English	US	Research	Economic decisions
41	Clark Jr CM et al. The potential role of diabetes guidelines in the reduction of medical injury and malpractice claims involving diabetes. Diabetes care 1994	English	US	Non-research	Judicial Decisions
42	Clark SL et al. Improved outcomes, fewer cesarean deliveries, and reduced litigation: results of a new paradigm in patient safety. American Journal of	English	US	Non-research	Judicial Decisions

	Obstetrics & Gynecology 2008				
43	Coleman RL. Promoting quality through managed care. American Journal of Medical Quality 1992	English	US	Non-research	Quality of Care
44	Coory M et al. Utility of routine data sources for feedback on the quality of cancer care: an assessment based on clinical practice guidelines. BMC Health Services Research 2009	English	Australia	Research	Other Health Policy/services/ management decisions
45	Covington MF et al. American College of Radiology Accreditation, Performance Metrics, Reimbursement, and Economic Considerations in Breast MR Imaging. Magnetic Resonance Imaging Clinics of North America 2018	English	US	Non-research	Medical education, certification and licensing
46	Crawley J et al. From evidence to action? Challenges to policy change and programme delivery for malaria in pregnancy. Lancet Infectious Diseases 2007	English	UK	Non-research	Other Health Policy/services/ management decisions
47	Currie CT et al. Audit, guidelines and standards: clinical governance for hip fracture care in Scotland. Disability & Rehabilitation 2005	English	UK	Research	Quality of Care
48	Daum W et al. Quality and outcome determination in health care and orthopaedics: evolution and current structure. Journal of the American Academy of Orthopaedic Surgeons 2000	English	US	Non-research	Quality of Care, Judicial Decisions
49	Davis D. Continuing education, guideline implementation, and the emerging transdisciplinary field of knowledge translation. Journal of Continuing Education in the Health Professions 2006	English	Canada	Non-research	Quality of Care, Medical education, certification and licensing

50	Davis DA et al. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. C.M.A.J. 157, 408–416 (1997).. CMAJ 1997	English	US	Research	Quality of Care, Economic decisions
51	de Bont A et al. Prioritisation by physicians in the Netherlands-The growth hormone example in drug reimbursement decisions. Health Policy 2007	English	Netherlands	Research	Economic decisions
52	de Pouvourville G. Quality of care initiatives in the French context. International Journal for Quality in Health Care 1997	English	France	Non-research	Quality of Care
53	Dickens BM. Malpractice liability implications of pacemaker and defibrillator guidelines in Canada. Cardiac Electrophysiology Review 2003	English	Canada	Non-research	Judicial Decisions
54	Dickens BM et al. The Judicial Decisions effects of fetal monitoring guidelines. International Journal of Gynaecology & Obstetrics 2010	English	US	Non-research	Judicial Decisions
55	Durieux P et al. From Clinical recommendations to Mandatory Practice. The introduction of regulatory Practice Guidelines in the French Health Care system. Int J health technology Assesmsnt in health Care 2000	English	France	Non-research	Quality of Care, Economic decisions
56	Durieux P et al. From clinical guidelines to quality assurance: the experience of Assistance Publique-Hopitaux de Paris. International Journal for Quality in Health Care 1997	English	France	Non-research	Quality of Care
57	Eddy DM. Practical Policies. What are they_. JAMA 1990	English	US	Non-research	Quality of Care, Economic decisions

58	Estes NA et al. Interdisciplinary strategies for arrhythmia program development: measuring quality, performance, and outcomes. Journal of Interventional Cardiac Electrophysiology 2011	English	US	Non-research	Quality of Care
59	Falstie-Jensen AM et al. Compliance with accreditation and recommended hospital care-a Danish nationwide population-based study. International Journal for Quality in Health Care 2017	English	Denmark	Research	Quality of Care
60	Fanous R et al. Hip fracture litigation: A 10-year review of NHS Litigation Authority data and the effect of national guidelines. Annals of the Royal College of Surgeons of England 2017	English	UK	Research	Judicial Decisions
61	Fearnley RA et al. Status of national guidelines in dictating individual clinical practice and defining negligence. British Journal of Anaesthesia 2012	English	UK	Non-research	Judicial Decisions
62	Field MJ. Overview: prospects and options for local and national guidelines in the courts. Joint Commission Journal on Quality Improvement 1993	English	US	Non-research	Judicial Decisions
63	Finder JM. The future of practice guidelines: should they constitute conclusive evidence of the standard of care?. Health Matrix 2000	English	US	Non-research	Judicial Decisions
64	Fluker SA et al. Incorporating performance improvement methods into a needs assessment: experience with a nutrition and exercise curriculum. Journal of General Internal Medicine 2010	English	US	Research	Medical education, certification and licensing
65	Frey K et al. The 'Collaborative Care' curriculum: an educational	English	US	Research	Medical education, certification and licensing

	model addressing key ACGME core competencies in primary care residency training. Medical Education 2003				
66	Gatterman MI et al. Chiropractic quality assurance: standards and guidelines. Journal of the Canadian Chiropractic Association 2001	English	Canada	Non-research	Quality of Care
67	Gerstein HC et al. A controlled evaluation of a national continuing medical education programme designed to improve family physicians' implementation of diabetes-specific clinical practice guidelines. Diabetic Medicine 1999	English	Canada	Research	Medical education, certification and licensing
68	Ghali JK et al. Heart failure guidelines, performance measures, and the practice of medicine: mind the gap. Journal of the American College of Cardiology 2010	English	US	Non-research	Quality of Care, Economic decisions
69	Ginsburg M et al. (De)constructing 'basic' benefits: citizens define the limits of Economic. Health Affairs 2006	English	US	Research	Economic decisions
70	Gonzalez F et al. Gonzalez F, Romero GA. Incorporación de Guías de Práctica Clínica en el Sistema Nacional de Salud ecuatoriano, como una estrategia para mejorar la salud y la educación médica. Revista de la Facultad de Ciencias Médicas (Quito). 2014;39(2):56-65.. Rev Fac Ciencias Med Quit 2014	Spanish	Ecuador	Non-research	Economic decisions, Medical education, certification and licensing
71	Gould BE et al. Teaching quality measurement and improvement, cost-effectiveness, and patient satisfaction in undergraduate medical education: the UME-21 experience. Family Medicine 2004	English	US	Research	Quality of Care, Medical education, certification and licensing

72	Groene O et al. Re-organisation of oesophago-gastric cancer services in England and Wales: a follow-up assessment of progress and remaining challenges. BMC Research Notes 2014	English	UK	Research	Other Health Policy/services/ management decisions
73	Grogan CM et al. How will we use clinical guidelines? The experience of Medicare carriers. Journal of Health Politics, Policy & Law 1994	English	US	Research	Economic decisions, Other Health Policy/services/ management decisions
74	Grol R. Standards of care or standard care? Guidelines in general practice. Scandinavian Journal of Primary Health Care - Supplement 1993	English	Netherlands	Non-research	Quality of Care, Economic decisions, Medical education, certification and licensing
75	Grol R. Improving the quality of medical care: building bridges among professional pride, payer profit, and patient satisfaction. JAMA 2001	English	Netherlands	Non-research	Quality of Care
76	Guest JF et al. Modelling the resource implications and budget impact of new reimbursement guidelines for the management of cow milk allergy in Finland. Current Medical Research and Opinion 2008	English	Finland	Research	Economic decisions
77	Guillod O. Clinical guidelines and professional liability: a short comment from the Judicial Decisions side. Orl; Journal of Oto-Rhino-Laryngology & its Related Specialties 2010	English	Swiitezerland	Non-research	Judicial Decisions
78	Hamashima Y et al. Development of hospital formulary in Japan-current trends and issues. Value in Health 2016	English	Japan	Research	Economic decisions
79	Tan H. Clinical practice guidelines: a critical review. International Journal of Health Care Quality Assurance 2006	English	Singapore	Non-research	Quality of Care, Medical education, certification and licensing, Judicial Decisions
80	Harvey IM et al. Clinical guidelines, medical litigation,	English	Uk	Non-research	Judicial Decisions

	and the current medical defence system. Lancet 1987				
81	Hayward RA et al. Quality improvement initiatives: issues in moving from diabetes guidelines to policy. Diabetes Care 2004	English	US	Non-research	Quality of Care
82	Hellbruck RP. Medical guidelines: a valid and reliable management tool?. International Journal of Health Planning & Management 1997	English	Germany	Non-research	Quality of Care
83	Herbert DL. Practice guidelines take center court: how to limit liability. Physician & Sportsmedicine 1996	English	US	Non-research	Judicial Decisions
84	Hirshfeld EB. Use of practice parameters as standards of care and in health care reform: a view from the American Medical Association. Joint Commission Journal on Quality Improvement 1993	English	US	Non-research	Other Health Policy/services/ management decisions, Judicial Decisions
85	Hirshfeld EB. Practice parameters versus outcome measurements. How will prospective and retrospective approaches to quality management fit together?. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition 1994	English	US	Non-research	Quality of Care, Judicial Decisions
86	Hoeks SE et al. Quality assurance in perioperative care. Best Practice & Research in Clinical Gastroenterology 2011	English	Netherlands	Non-research	Quality of Care
87	Hoge MA et al. Best practices in behavioral health workforce education and training. Admin Pol Mental Health 2004	English	US	Non-research	Medical education, certification and licensing
88	Hughes E. Two cheers for clinical practice guidelines: the hopes and headaches of quality improvement in	English	Canada	Non-research	Quality of Care

	reproductive healthcare. Human Reproduction 2011				
89	Hurwitz B. Clinical guidelines and the law: advice, guidance or regulation?. Journal of Evaluation in Clinical Practice 1995	English	UK	Non-research	Judicial Decisions
90	Hurwitz B. Clinical guidelines tensions--a Judicial Decisions perspective. Commentary on 'Clinical guidelines: ways ahead'. Journal of Evaluation in Clinical Practice 1998	English	UK	Non-research	Judicial Decisions
91	Hurwitz B. Judicial Decisions and political considerations of clinical practice guidelines. BMJ 1999	English	UK	Non-research	Judicial Decisions
92	Huttin C. The use of clinical guidelines to improve medical practice: main issues in the United States. International Journal for Quality in Health Care 1997	English	US	Non-research	Quality of Care, Economic decisions, Judicial Decisions
93	Hyams AL et al. Practice guidelines and malpractice litigation: a two-way street. Annals of Internal Medicine 1995	English	US	Research	Judicial Decisions
94	Hyams AL et al. Medical practice guidelines in malpractice litigation: an early retrospective. Journal of Health Politics, Policy & Law 1996	English	US	Research	Judicial Decisions
95	Jacobson PD. Judicial Decisions and policy considerations in using clinical practice guidelines. American Journal of Cardiology 1997	English	US	Non-research	Judicial Decisions
96	Jacobson PD. Transforming Clinical Practice Guidelines Into Legislative Mandates Proceed With Abundant Caution. JAMA 2008	English	US	Non-research	Judicial Decisions
97	Jutras D. Clinical practice guidelines as Judicial Decisions norms. CMAJ Canadian Medical Association Journal 1993	English	US	Non-research	Judicial Decisions

98	Kahn JM et al. An official American thoracic society workshop report: developing performance measures from clinical practice guidelines. Annals of the American Thoracic Society 2014	English	US	Non-research	Quality of Care, Economic decisions
99	Kahn JM et al. An official American Thoracic Society policy statement: pay-for-performance in pulmonary, critical care, and sleep medicine. American Journal of Respiratory & Critical Care Medicine 2010	English	US	Non-research	Quality of Care
100	Kapp, MB. The Judicial Decisions status of clinical practice parameters: an annotated bibliography. American Journal of Medical Quality 1993	English	US		Judicial Decisions
101	Kaufman JM. Negotiating with payers. Neurologic Clinics 2010	English	US	Non-research	Economic decisions
102	Kessler DP. Evaluating the medical malpractice system and options for reform. Journal of Economic Perspectives 2011	English	US	Non-research	Economic decisions
103	Keyes GG. The Judicial Decisions implications of clinical practice guidelines. Journal of the American Dental Association 1996	English	US	Non-research	Economic decisions
104	Kibbe DC et al. Integrating guidelines with continuous quality improvement: doing the right thing the right way to achieve the right goals. Joint Commission Journal on Quality Improvement 1994	English	US	Non-research	Quality of Care, Economic decisions, Medical education, certification and licensing
105	Kiser JJ. Practice guidelines: development, application to clinical care, and role in provider education. Clinical Pharmacology & Therapeutics 2009	English	US	Non-research	Economic decisions, Medical education, certification and licensing
106	Kliger AS. Clinical practice guidelines and performance measures in ESRD. American	English	US	Non-research	Quality of Care

	Journal of Kidney Diseases 1998				
107	Kluge EH. Clinical practice guidelines and the law. CMAJ Canadian Medical Association Journal 1996	English	Canada	Non-research	Judicial Decisions
108	Kosimbei G et al. Do clinical guidelines reduce clinician dependent costs?. Health research policy and systems 2011	English	Kenya	Research	Economic decisions
109	Kowalski C et al. Quality of care in breast cancer centers: results of benchmarking by the German Cancer Society and German Society for Breast Diseases. Breast 2015	English	Germany	Research	Quality of Care, Other Health Policy/services/ management decisions
110	Lameire N et al. Lameire N, Van Biesen W. Clinical practice guidelines: an important tool in improving dialysis quality. InPeritoneal Dialysis-State-of-the-Art 2012 2012 (Vol. 178, pp. 58-67). Karger Publishers.. Peritoneal Dialysis – State-of-the-Art 2012	English	Belgium	Non-research	Quality of Care
111	Lanier DC et al. Doctor performance and public accountability. Lancet 2003	English	US, UK, Netherlands	Non-research	Quality of Care
112	Larriviere DG et al. Invited Article: Threats to physician autonomy in a performance-based reimbursement system. Neurology 2008	English	US	Non-research	Economic decisions
113	Lavelle C et al. The role of clinical guidelines in controlling expenditures for dental care. Journal (Canadian Dental Association) 2002	English	Canada	Non-research	Judicial Decisions
114	Lawler PR et al. Clinical Practice Guidelines as Instruments for Sound Health Care Priority Setting. American Journal of Cardiology 2015	English	US	Non-research	Other Health Policy/services/ management decisions
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CHAPTER 3: ROLES OF CLINICAL PRACTICE GUIDELINES OUTSIDE THE CLINICAL ENCOUNTER: AN INTERNATIONAL SURVEY OF GUIDELINES DEVELOPERS

Chapter 3: Roles of Clinical Practice Guidelines outside the clinical encounter: An International Survey of Guidelines Developers

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Abstract

Background: Clinical practice guidelines (CPGs) are increasingly used to inform and support decisions outside the clinical encounter. Our aim was to describe how CPGs play roles outside the clinical encounter from the perspective of international guideline developers.

Methods: We administered an online survey to organizations or groups that produce CPGs. Survey questions focused on the characteristics of the organization/group, methodological approaches to development, and the frequency by which CPGs were used to inform decisions and processes outside the clinical encounter. We used a previously tested 11-item list of potential CPGs roles, independent of the clinical encounter and summarized the results using descriptive statistics.

Results: We received responses from 78 organizations from 32 countries (34.7% overall response rate), split evenly among CPG producers from government, professional societies, and other (e.g. universities). Seventy-five organizations (96.1%) reported that their CPGs are used in activities aimed to improve quality of care (quality improvement processes, or development of quality indicators or standards) and 33 (42.3%) reported role on drug coverage decisions. We found that CPGs also play roles in health professional education (75.6%) and continuing medical education (60.2%). The role of CPGs in research prioritization activities was also reported by most of the organizations (70.5%). Moreover, 23 organizations (29.5%) reported their CPGs were used for judicial decisions. Most of the organizations reported that these roles are part of their CPGs aims and stakeholders in charge of these activities are considered among their target users. Quality of care functions were more frequently reported as a role by organizations from high-income countries, while judicial functions was more frequently reported by organizations that produce a high volume of CPGs.

Conclusion: CPGs are commonly used for informing activities aimed to improve quality of care, to support coverage decisions, to inform research prioritization, and for medical education activities but not as commonly, while informing judicial decisions was less frequently reported. CPGs are informing many decisions outside the clinical encounter.

Background

Clinical practice guidelines (CPGs) are statements that include recommendations intended to optimize patient care, which should be informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (1, 2). CPGs have traditionally been used to assist in clinical decision-making, that is, to support decisions made between clinicians and patients, such as the use of interventions or diagnostic procedures for patients (1, 2). However, CPGs have been increasingly used for decisions by stakeholders outside the clinical encounter.

The interest in CPGs increased in the 1980s in many developed countries because they were identified as potential tools for addressing problems in the health care systems, such as rising healthcare costs; the rapid emergence of new expensive technologies; inappropriate variations in service delivery among providers and hospitals, and across geographical regions (3); and the intrinsic desire of healthcare professionals to offer, and of patients to receive, the best care possible (4). Consequently, recommendations from guidelines have been used to guide quality improvement processes, to inform drug coverage decisions and reimbursement decisions at the national-level (economic decisions), and to identify health research gaps, among others(4).

The different roles of CPG outside the clinical encounter have been a neglected area of inquiry. Therefore, understanding the current uses of CPG by different stakeholders and the purposes, successes and failures in their application, will improve the knowledge about the potential impact on health care. Moreover, it will also provide insights into better strategies to develop and disseminate them to optimize their benefit and impact. For example, should different roles for their use impact on the guideline panel composition, how the guideline scope and questions are defined, and how recommendations should be framed and characterized to make them useful.

Our team recently conducted a critical interpretive synthesis to summarize and describe CPGs use outside of the clinical encounter, and we developed a framework(5). We identified several potential roles of

CPGS outside the clinical encounter decisions, that we categorized under two main overarching goals (quality and economic decisions), two secondary roles (research prioritization and education/licensing and certification), and one consequence role (judicial decisions). With this framework, we sought to explore the range of roles CPGs currently play in the community and if some options were prevalent than others.

Since developers control most of the process from the guideline conception until its final output, they are key actors in the content of the CPGs recommendations. Although they may not necessarily be in charge of dissemination and implementation activities, these organizations represent a good proxy when interested in understanding the roles of CPGs in different contexts. Our aim was to describe the roles of CPGs outside the clinical encounter form the perspective of international guideline developers and describe how frequent developers, consider that their CPGs recommendations are used for these roles

Methodology

Design and ethical approval

We used a cross-sectional design (Online Survey). The McMaster Hamilton Integrated Research Ethics Board (hireb.ca) approved the study (Project #7945, November 2019). Individuals representing CPG development groups to whom we sent an invitation email gave implied informed consent by clicking on the link to access the survey and completing it.

Population

We invited organizations and groups that develop guidelines (developers). The sample of candidate participants was created from the Guidelines International Network (an international non- profit association that includes of organizations from all over the world involved in developing and implementing guidelines) membership list (http://www.g-i-n.net); the list of developers provided by the Guidelines Central website (https://www.guidelinecentral.com); and from an asset map developed by the SPOR evidence alliance of

CPGs produced in Canada(6). We also considered organizations that were known to be producing guidelines in different countries and were not covered by the previous resources.

Procedures

In each organization we identified the key contact persons, including directors, coordinators or guideline methodologists. Contact information was obtained from the database of the organizations described or their websites. The email provided information about the project, the ethical approval, and the investigators' contact information. We asked key contacts to provide information on the best person to reach out, or alternatively, to forward the email invitation to them. In some cases, key contacts asked for an electronic version of the survey to decide who would be the best person to answer according to the survey's scope. We distributed the invitation emails in February and March 2020 and sent two reminder emails between April and May 2020. We closed the survey on May 30th, 2020.

Instrument

We designed a self-administered survey with fifteen questions that explored two dimensions. First, we explored the characteristics of the organization and their CPG development: the number of CPGs produced annually; type of organization (e.g., government-related, professional/scientific societies, patients' associations, health care providers, others); type(s) of evidence product(s) produced by the organizations (CPGs, systematic reviews, health technology assessments, others); whether costs and cost-effectiveness analyses were included in their methods and guidance documents;, and the degree of government's participation of in the CPG development. Second, we asked developers to state if their guidelines commonly played a role on each one of the preestablished list of eleven activities and decisions. This list was built based on the results from our framework that categorizes them in two primary goals outside the clinical encounter (quality and economic decisions), two secondary goals (education and licensing, and research prioritization) and one consequence role (judicial decisions) (5). We designed an online survey using the

LimeSurvey software (LimeSurvey GmbH, Hamburg, Germany). The survey was piloted with three organizations and we made adjustments to improve its understanding.

Analysis

We used descriptive statistics to analyze the variables. Numeric variables are presented as median and inter-quartile ranges (IQR), and non-numeric variables as frequencies and proportions. We described the organizations' characteristics and key CPG methodological approaches reported by developers. We used the World Bank Classification 2020 (7) to categorize countries as high-income or low-middle income countries. We also described the frequency developers reported each of the 11 preidentified roles and any additional role (5)(roles), the frequency they reported these roles were considered as CPGs aims (aims), and the frequency they considered groups or organizations in charge of those activities as target users of their CPGs (target users). We also calculated the frequency of the roles categorize and grouped according to CPGs' major goals we have previously described: quality, coverage, education/licensing, research prioritization and judicial decisions.

We performed bivariate analysis to explore variables (i.e., organization's characteristics and the CPG methodological approaches) that could be associated to the presence of different roles. For this purpose, we used the with Fisher exact test for categorical variables and the U Mann Whitney test for continuous variables that did not present a normal distribution. A p-value <0.05 was considered as threshold for making chance an unlikely explanation of observed differences. Data analysis was performed using Stata 15.0 statistical software. (Stata Corp., College Station, Texas).

Results

Respondents

We invited 198 organizations and groups. We received three email responses declining their participation, and we obtained a total of 98 survey responses. We got one duplicate response (two respondents from the same organizations, in which case we only considered the first survey answered) and 19 incomplete surveys, which were excluded. We obtained full responses from 78 organizations, after sending three reminders over a three months period. The final response rate was 39.4%.

The full list of the organizations that participated is detailed in appendix 2. The characteristics of the organizations that responded to the survey are presented in table 1. We received responses from developers in 32 countries representing six continents. Respondents from the United States, Netherlands, Canada, Australia and Belgium the most common ones. More than half of organizations were from North America or Europe, and five (6.4%) of them were from international organizations or organizations that reflected a collaboration between more than one country. The organizations had produced a median of 17 CPGs (IQR 5-40). Approximately one-third of organizations were government-related, one third were professional societies, and the rest (i.e. other) were a mix of universities, hospitals, insurance companies, and not for profit independent organizations that produce CPGs for third parties.

Only 15 (19.2%) of organizations declared that the production of CPGs and other evidence-based products is their main aim, which means that the rest have a more comprehensive suite of activities in the health system. Government funding, partial or total, for supporting CPGs development occurs in 40 (51.2%) of the organizations. Approximately half of the government organizations participate in CPG topic prioritization, the development process itself, or in the approval of recommendations. Cost considerations are included in the CPG development in some way by 62 organizations (83.3%).

CPGs roles

Regarding the role of CPGs in quality-related activities, the majority of organizations reported that CPGs play roles in them. Seventy-five organizations (96.1%) reported that their CPGs are used in at least one role related to activities aimed to improve quality of care. In general, most of them reported that CPGs play roles in quality improvement processes, the development of quality indicators or the development of quality standards. The role of CPGs in the development of performance incentives or in accreditation activities was less commonly reported. The role of CPGs in coverage decisions was reported less frequently than in quality-related activities. Thirty-three organizations (42.3%) reported that their CPGs play some role in coverage decisions in their contexts.

We found that CPGs also frequently play roles in health professional education (75.6%) and continuing medical education (60.2%). In contrast, the role of CPGs in licensing and maintenance of certification was reported by only 12 organizations (15.4%). Lastly, the role of CPGs in research prioritization activities was also reported by most of the organizations (70.5%), while in judicial decisions CPGs role was reported by only 23 organizations (29.5%).

Five organizations (6.4%) reported at least one role different to the 11 we suggested in our survey (see appendix 3 for a summary of additional roles or activities). Almost all of them were considered as falling into the predefined clinical encounter decisions role (clinician or patients' decisions), or as implementation activities. The other roles reported by participants: *"integration in computer systems"* and "*inform disease management programs, organize coordination of care between sectors",* were considered under our previously developed category(5) health policy/services/ management decisions.

We also asked organizations whether they consider these activities as one of their CPGs aims, and whether stakeholders responsible for these activities were identified as target users of their CPGs. The proportion of organizations that reported their CPGs are aimed to inform these activities were very similar

to the reported frequency of those roles (range from 19.2% for education/licensing to 88.5% for quality improvement activities) (Table 2). Also, the reported proportions of organizations considering that stakeholders responsible for these activities were identified target users of the CPGs were also very similar to the reported frequency of those roles (range from 23.1% for education/licensing to 87.2% for quality improvement activities). The only exception was the health professional's education role. Although 59 (75.6%) organizations considered that CPGs play a role in these activities, only 35 (44.9%) considered people in charge of them (e.g., instructors and teachers in medical schools or hospitals) were their target users.

We explored the differences between organizations according to the presence or not of the major roles (quality, coverage, research prioritization, education and licensing and judicial decisions) according to different organizations' characteristics (table 3). The role of CPGs to inform quality of care activities was reported by all the organizations in high-income countries, while in those from low and middle-income countries, and international organizations CPGs were not informing quality of care in all the cases (p=0.018). Also, the role of CPGs in judicial decisions was more frequently reported by organizations with a larger number of CPGs produced (p=0.003). We did not find any additional differences between the report of the role or not according to the rest of organizations' characteristics.

Discussion

Principal findings

In this international survey of CPGs developers, we found that all the organizations reported at least one role of CPGs outside the clinical encounter decisions. The most frequent roles were those related to activities and processes focused on improving the quality of care, i.e., in quality improvement activities and in the development of quality standards or quality indicators. Almost half of the organizations reported that CPGs play a role in informing coverage decisions. Moreover, CPGs had several secondary goals:

educational and licensing activities (66 organizations, 84.6%), and research prioritization activities (55 organizations; 70.5%). Finally, the role of CPGs in judicial decisions was reported by only 23 organizations (29.5%).

In most of the cases, organizations reported specific roles of CPGs, and they reported that those roles were considered aims of their CPGs and that organizations or groups in charge of those activities were considered target users of their CPGs. The only role in which we found a difference between its reporting and the frequency in which organizations considered teams or organizations as target users were in medical education. Developers reported that their CPGs are regularly used as tools in health professionals' education (75.6%), although medical teachers or clinician-educators were considered target users of their CPGs in only 44.6% of the cases.

The finding that the vast majority of organizations and groups reported that CPGs play some roles in activities and processes focused on improving the quality of care is not surprising. In our critical interpretive synthesis, we also found that this was the most common role described in the literature(5). Among all the possible roles in the quality of care, developing indicators and standards are the most common ones, while accreditation activities and developing performance incentives were less common.

CPG developed to inform economic decisions, as coverage decisions, was less commonly mentioned. This role has been less studied and reported. Although we did not find any organization's characteristic associated with the presence of this role, literature has suggested that it may occur in organizations that have experience in developing HTA and CEA(5). This role, although extensively suggested in the literature requires more research, since almost half of the organizations described it and its presence seemed to be associated neither with the incorporation of costs or economic evidence in the CPGs nor with the development of HTA in these organizations.

We have argued that the potential of CPGs to identify research gaps and to support research prioritization activities is promising and any activity to facilitate the link between the CPGs and the research funders will be beneficial to reduce relevant knowledge gap. Finding that almost three-quarters of

organizations consider their recommendations are used in these activities is motivating. However, the exact way these CPG play a role and how much they succeed in these activities might be a matter of further research.

Findings in relation to other studies

We did not identify studies that had investigated how frequent CPGs play roles outside the clinical encounter. Most of the literature that discusses these potential CPGs roles are narrative reviews, discussion papers, editorial or letters. A critical interpretive synthesis we conducted, which provides the foundations for designing our survey is the only available study that we are aware of.

Many surveys focused on guidelines organizations have been developed. However, most of them have focused on specific methodological and developmental approaches (8, 9), on methods for guidelines updating(10), or for incorporating patients preferences(11). However, Burgers et al. almost two decades ago, investigated the structure and working methods of 18 guidelines programs(8). Among all the questions considered, authors asked about the target users of their CPGs. They found that out of the 18 organizations, 9 of them explicitly described that policymakers were among their target users, 8 of them stated that cost-containment or cost-effectiveness was one of their objectives and, one of them stated that organization of health services was one of their objectives. Thus, the roles of CPGs beyond informing clinical decisions has been one of the aims of international organizations for decades.

Finally, few studies have studied how much CPG might be used or are aimed to inform some policy decisions. In a survey to decision-makers from Canadian provincial health ministries, regional health authorities and hospitals, Ouimet et al. found that CPGs were more used by hospital's managers, than by decision makers in Ministries or public agencies. One-third of the latter reported that they have rarely or have never used CPGs in their daily activities, while in among hospital managers this was the case in only 21% of the respondents. However, authors did not explore how CPGs were used.

Gagliardi et al. created a framework that may support CPGs implementability(12). Authors applied the framework to selected CPGs on topics representing a high burden of illness in primary and institutional care. Authors found that of 20 CPGs, all of them stated that their aim was to inform clinical decisions, while only one and two stated that their aim was to inform quality and education, respectively. None of the CPGs stated their recommendations had the objective to inform policy. Although this was a very small sample size of CPGs, it seems CPGs are not commonly stating that informing decisions outside of the clinical encounter is one of their aims. This contrast to our results, as most of the survey respondents clearly stated that stakeholders in charge of many activities related to quality, economic decisions, education or research prioritization are their objective and target users.

Strengths and limitations

Our study has several strengths. First, our survey was developed based on a framework that was derived from a previously conducted critical interpretive synthesis. Moreover, we received responses from organizations that produce CPGs globally regardless of their funding, or scope, including low- and middle-income countries. Our sample was composed of both government-related organizations and professional or scientific societies, among others. Most of the organizations had produced more than 10 CPGs, and their funding came from different sources, such as government and their own professional societies resources. Also, our response rate was 39.4%, which is acceptable considering that the survey's responses rates are commonly lower than this number.

However, our work also has limitations. Our sample size was limited for some analyses which reduces our ability to detect differences. Also, it is important to state that we only studied the perceptions of some key individuals that are part of guideline organizations and groups that produce CPGs. Although we made efforts in trying to identify "the best respondent". It may happen that developers do not know the real roles and uses of their CPGs. For instance, to determine the real role of CPGs in activities focused in improving quality of care is to focus on quality improvement, quality standards, or accreditation experts, or on drug funding decision-makers (to determine the role in coverage decisions), or on medical school

teachers, research funders and on medical litigation lawyers and judges. Moreover, although developers stated that CPGs play all these roles and they considered the mentioned stakeholders as they target users, we do not know to what extent these uses are explicitly stated as such, in their CPGs documents.

Implications for policy and practice

Our work is critical for developers and decision-makers. Developers now have an overview of how frequent CPGs may play a role in the different activities we covered. Our findings will help in planning guidelines development and in focusing the CPGs scope and the when writing the final recommendations and CPGs report. Developers might also consider our results useful for defining their CPGs' aims and their target users, including broadening or limiting their scope. Decision-makers can use these results when determining the potential scope of their guidelines programs.

CPGs provide recommendations to inform clinical decisions, but we have shown how developers consider CPGs play many other roles outside that context. Considering that recommendations are traditionally targeted to inform clinical decisions, but at the same time developers reported all these roles are frequent and they develop guidelines with the aim of informing them as well. We think this issue requires more attention.

Although the considered CPGs are aimed to inform many roles, and they targeted stakeholders in charge of them, it is still not clear whether CPGs should continue being seen as recommendations mainly aimed to inform clinical decision but also with many other roles as secondary aims, or they have been pushed or forced to meet these other goals to which they were not originally developed. It might be that these roles largely depend on the context. Also, to date, there is neither enough evidence on how useful different stakeholders consider CPGs are for their activities nor on how CPGs play those roles activities. For instance, it is not clear whether CPGs inform coverage decisions through their recommendations, or through other components such as the guidelines questions, providing evidence synthesis of making suggestions to

coverage decision-makers. Moreover, it is not clear if CPGs need to be modified as a response to better fit those aims.

Finally, we did not find any association between the government influence either when analyzing the organizations' characteristics (government related or not), or when considering the participation of governments in the CPG development. However, our analysis was just a first approach to the relationship between developers and government. It seems the degree of governments' involvement in the CPG development does not associate with the roles we have studied, at least from the developer's perspective. Moreover, regardless of the government' involvement, it is not clear how much, and how, ministries and other government-related organizations use CPGs to support some of their decisions.

Implications for future research

Further research focused on specific roles that were reported by most of the organizations such as research prioritization, and medical education is required. Moreover, although it was not reported by most of the organizations and groups, the role of CPGs in informing or supporting coverage decisions should be a matter of further research. The role of CPGs in these decisions, although described in the literature for decades, is not clear enough and it might be challenging to transfer clinical recommendations to economic and coverage decisions. Also, some research focused on the target users is needed for understanding how CPGs play a role some of these activities, such as in judicial decisions.

Conclusions

Our survey found that CPGs are playing many roles outside the clinical encounter decisions. Developers reported that CPGs are commonly used for informing activities aimed to improve quality of care, to support coverage decisions, to inform research prioritization, and medical education activities. The

role of CPGs in judicial decisions was less frequently reported. Developers also reported that these roles were considered one of the aims of their guidelines, and they target users from these fields when developing their CPGs. Overall, these results highlight that CPGs have roles beyond the clinical encounter and that they seem to occur in the vast majority of contexts and developers commonly target users according to these activities. CPGs, although mainly focused on supporting clinical decisions, they are informing many other decisions. CPG developers need to have this in mind when crafting and implementing their recommendations.

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Table 1: CPGs Organizations' Demographics

Organization's Characteristics	Frequency (%)
Geographic Location	
Europe	23 (29.9)
North America	21 (26.9)
Asia	14 (17.9)
Central and South America	5 (6.4)
Africa	5 (6.4)
Oceania	5 (6.4)
International	5 (6.4)
Total number of CPGs produced	
<10	28 (35.9)
11-50	32 (41)
>50	13 (16.7)
Not reported	6 (6.4)
Organization type	
Government related	23 (29.5)
Professional or scientific societies	28 (35.9)
University, hospitals or health insurance organizations	11 (14.1)
Others (patients, industry, NGOs)	12 (15.4)
Mixed	4 (5.1)
Organization's main aim	
Producing CPGs and other products is a major aim	15 (19.2)
Produce CPGs and others, is not the major aim	63 (80.8)
Guidelines funding	
Government only	26 (33.3)
Professional or scientific societies	23 (29.5)
Mixed (Government + other bodies)	13 (16.7)
Others	16 (20.5)
Evidence-based resources produced	
CPGs only	31 (39.7)
CPG and types of reviews (systematic, scoping, etc.)	24 (30.7)
CPGs and HTAs	23 (29.5)

Guideline development approach	
De novo development and other approaches	47 (60.2)
Only de novo development	16 (20.5)
Only adaptation	7 (9.0)
Only endorsement	8 (10.3)
Methods for quality assessment of the evidence	
GRADE approach	48 (61.5)
Combination of methods	17 (21.8)
Other methods/approaches	3 (3.8)
Not reported	10 (12.8)
Methods for quality assessment of CPGs reviewed/adapted	
AGREE tool	48 (61.5)
Combination of methods	17 (21.8)
Other methods/approaches	3 (3.8)
Not reported	10 (12.8)
Methods for considering costs and economic evidence	
Use of some evidence on costs (No CEA)	29 (37.2)
Conduct literature reviews or identify known CEA	18 (23.1)
No costs considered	13 (16.7)
Develop their own CEA	9 (11.5)
Others (Not applicable, costs are subjective)	9 (11.5)
Involvement of government bodies in CPG development	
No participation	29 (37.2)
Prioritization, scope or questions definitions or all steps	31 (39.7)
Recommendations' review or approval	8 (10.3)
Others (sometimes, some members may sometimes participate)	10 (12.8)

AGREE: Appraisal of Guidelines for REsearch & Evaluation tool; CEA: Cost-effectiveness analyses; CPG: Clinical practice guidelines; HTA: GRADE: Grading of Recommendations, Assessment, Development and Evaluations approach; Health Technology Assessment;

Table 2. Types and Frequency of Roles of CPGS reported by organizations

	CPGs play a role in these activities N (%)	One of CPGs aims is to inform these activities§ N (%)	One of the target users of CPGs are individuals or groups in charge of these activities§ N (%)
Quality¶	**75 (96.1)**	**69 (88.5)**	**68 (87.2)**
Quality improvement activities	68 (87.2)	66 (84.6)	60 (76.9)
Quality standards development	43(55.1)	41 (52.6)	43 (55.1)
Quality indicators	53 (67.9)	58 (74.4)	55 (70.5)
Performance incentives development	10 (12.8)	11 (14.1)	14 (17.9)
Accreditation	22 (28.2)	18 (23.1)	23 (29.5)
Coverage/Economic decisions	**33 (42.3)**	**34 (43.6)**	**35 (44.9)**
Educational/licensing activities¶	**66 (84.6)**	**64 (82.1)**	**62 (79.5)**
Health professionals' education	59 (75.6)	55 (70.5)	35 (44.9)
Continuing medical education	47 (60.2)	41 (52.6)	57 (73.1)
Licensing/maintenance of certification	12 (15.4)	15 (19.2)	18 (23.1)
Research prioritization	**55 (70.5)**	**57 (73.1)**	**49 (62.8)**
Judicial decisions	**23 (29.5)**	**19 (24.4)**	**20 (25.6)**
Other health policy/services/ management decisions	**2 (2.5)**	**2 (2.5)**	**2 (2.5)**

§ Includes those organizations that responded to the question with "Yes" or "sometimes"
¶ Major roles "Quality" and "Educational/licensing activities" include organizations that reported at least one of the specific roles that are part of each category (presented in the row below each one of them)

Table 3: Differences between the reported major roles according to organizations' characteristics

	Quality of care activities			Coverage/Economic decisions			Education & Licensing			Research prioritization			Judicial decisions		
	Yes (n=75)	No (n=3)	P value¶	Yes (n=33)	No (n=45)	P value¶	Yes (n=66)	No (n=12)	P value¶	Yes (n=55)	No (n=23)	P value¶	Yes (n=23)	No (n=55)	P value¶
Number of CPGs produced†	15 (5-45)	30(17-36)	0.45	17 (7.5-5)	15(5-36)	0.238	15 (5-36)	32.5 (10-72)	0.187	18 (7-40)	12.5 (4-45)	0.85	28.5(8-100)	5 (15-36)	**0.003**
Country's classification‡															
High Income	54 (100)	0 (0)	**0.018**	24 (44.4)	30 (56.6)	0.571	45 (83.3)	9 (16.7)	0.143	36 (66.6)	18 (33.4)	0.535	18 (33.4)	36 (66.6)	0.535
Low and Middle Income	17 (89.5)	2 (10.53)		8 (42.1)	2 (57.9)		18 (94.7)	1 (5.26)		15 (78.9)	4 (21.1)		4 (21.1)	15 (78.9)	
International	4 (80)	1(20)		1 (20)	4 (80)		3 (60)	2 (40)		4 (80)	1 (20)		4 (80)	1 (20)	
Type of organization‡															
Government related	22 (95.6)	1 (4.3)	0.357	10 (43.5)	13 (56.5)	0.661	19 (82.6)	4 (17.4)	0.689	15 (65.2)	8 (34.8)	0.748	7 (30.4)	16 (59.6)	0.789
Societies	28 (100)	0 (0)		9 (32.2)	19 (67.8)		25 (89.3)	3 (10.7)		21 (75)	7 (25)		7 (25)	21 (75)	
Others	25 (92.6)	2 (7.4)		14(48.2)	13(51.8)		22 (81.5)	5 (18.5)		19 (70.4)	8 (29.6)		9 (23.3)	18 (76.7)	
Organization's aim is only to produce CPGs/evidence products‡															
Yes	15 (100)	0 (0)	0.389	9 (60)	6 (40)	0.661	14 (93.3)	1 (6.6)	0.298	11 (63.6)	4 (36.4)	0.79	4 (36.4)	11 (63.6)	0.79
No	60 (95.2)	3 (4.8)		24 (38)	39 (62)		52 (82.5)	11 (17.5)		44 (69.8)	19 (30.2)		19 (30.2)	44 (69.8)	
Type of evidence products‡															
CPGs and other products	53 (96.4)	2 (3.6)	0.88	25 (45.4)	35 (54.6)	0.384	45 (81.8)	10(18.1)	0.29	40 (72.7)	15 (27.8)	0.507	19 (34.5)	36 (56.5)	0.13
CPGs and HTA	22 (95.6)	1 (4.4)		8 (34.8)	15 (65.2)		21 (91.3)	2 (8.7)		15 (65.2)	8 (34.8)		4 (17.42)	19 (82.8)	
Funding‡															
Government	37 (94.9)	2 (5.1)	0.661	18 (46.1)	21 (53.9)	0.676	32 (82)	7 (18)	0.569	28 (71.8)	11 (28.2)	0.968	13 (33.3)	26 (66.7)	0.303
Societies	22 (95.7)	1 (4.4)		8 (34.8)	15 (65.2)		21 (91.3)	2 (8.7)		16 (69.5)	7 (30.5)		4 (17.4)	19 (82.6)	
Others	16 (100)	0 (0)		7 (43.7)	9 (56.3)		13 (81.2)	3 (18.7)		11 (68.7)	9 (31.2)		6 (37.5)	10 (62.5)	
Regular consideration of Cost/Economic evidence‡															
Yes	62 (95.4)	3 (4.6)	0.43	57 (87.7)	8 (12.3)	0.762	55 (84.6)	10 (15.4)	1.0	49 (65.4)	16 (34.6)	0.05	19 (29.23	46 (70.8)	0.912
No	13(100)	0 (0)		11(84.6)	2(15.4)		11 (84.6)	2 (15.4)		6 (46.1)	7 (53.9)		4 (30.77	9 (69.23	
Government's participation in the CPG development‡															
No participation	29 (100)	0 (0)		11(37.9)	18 (62.1)	0.547	24 (82.7)	5 (17.2)	0.73	21 (72.4)	8 (27.6)	0.777	11 (37.9)	18 (62.1)	0.208
In some or in all the steps	46 (93.9)	3 (6.1)		22 (44.9)	27 (55.1)		42 (85.7)	7 (14.3)		22 (71.4)	27 (30.6)		12 (24.5)	37 (76.5)	

† data presented in median (IQR); ‡ data presented in # (%); ¶Fisher's exact test. CPG: Clinical practice guidelines; HTA: Health Technology Assessment

Appendices

Appendix 1. Questionnaire

Appendix 2. Full list of organizations that participated in the survey

Appendix 3: Additional reported roles and quotes from organizations

Appendix 1. Questionnaire

Introductory questions:

Throughout this survey, the following acronyms and labels will be used.

CPG = clinical practice guideline; SR = systematic review; HTA = health technology assessment; Advice Products = generic term to refer to CPGs, SRs, and/or HTAs.

Link to the Online Survey (Lime Survey: https://surveys.mcmaster.ca/limesurvey/index.php/456666?lang=en)

Organizational descriptors

- Organization Name
- CPG program name (if different from the overall organization name)
- Province/State/Region and Country
- Number of CPGs produced

1. Indicate the best descriptor for your organization.

a. Ministry of Health or other government division.

b. Public agency, affiliated with, but arms-length from, national or provincial/state government.

c. Professional or medical association/society

d. Academic program affiliated with a university.

e. Patient or consumer organization.

f. Independent or private organization.

g. Other, please specify_____

2. Indicate the option that best describes your organization's scope of activities.

a. The organization's sole responsibility is to develop advice products such as CPGs, SRs, HTAs, etc.
b. Developing advice products is one of the many roles of the organization. For example, CPGs, SR and HTA activities may represent a program or team within the larger organization. The organization is responsible for other activities such as monitoring quality, education, making funding recommendations, making funding decisions.
c. Other. Please specify_____

3. Indicate the types of advice products developed/endorsed or adapted by your organization (click all that apply).

a. CPG.
b. SR (including rapid reviews/responses)
c. HTA.
d. Other (please specify) _____
e. Our organization does not develop, endorse or adapt advice products.

4. Indicate health issues addressed in your advice products.

a. Disease or clinical condition specific (please specify) _____
b. All diseases.

5. Indicate the care trajectory stages addressed by your advice products.

a. Public health or prevention
b. Screening.
c. Diagnostic.
d. Treatment.
e. Rehabilitation
f. End-of-life or palliative care

g. Health services or health systems

h. Other

6. How is the guideline development process funded?

*Please select all the bodies/organizations that directly finance (partial or totally) the guideline development process. If your organization is a private party, please mark all for those you have develop or supported guidelines processes***)**

a. Government (includes: Ministries, HTA agencies, regulatory agencies, national institutes, research institutes, etc.)

b. Professional or medical societies

c. Universities (e.g., via grants)

d. Patients advocates associations

e. Pharmaceutical/devices/food industry

f. Others. Please specify_____

g. Do not know/not sure_____

7. Indicate the method(s) used in CPG development (check all that apply).

a. De novo CPG development.

b. Adapt CPGs from other organizations.

c. Endorse CPGs from other organizations.

d. Our role does not include CPG development, or development of any advice products.

e. Our role does not include CPG development but does include development of other advice products such as HTAs.

f. Other (please specify)

8. Indicate the method(s) used to assess the quality of the evidence in development of de novo CPGs.

a. GRADE approach.
b. Cochrane Risk of Bias.
c. Other tool(s) (please specify) _____
d. We do not assess the quality of the evidence in the development of CPGs.
e. We do not do de novo CPGs development (we use the method used in the Guidelines we adopt/adapt/endorse)

9. Indicate the method(s) used to assess the quality of existing CPGs in adaptation or endorsement activities.

a) AGREE II.
b) IOM Standards.
c) GIN Assessment Tool.
d) Other, please specify_____
e) We do not assess the quality of existing CPGs in adaptation or endorsement activities.
f) We do not adapt or endorse existing CPGs.

10. Do you regularly use cost-effectiveness evidence in your Guideline process?

a. Develop your own cost-effectiveness analysis as part of the process for some key recommendations
b. Perform systematic reviews of available/published cost-effectiveness analyses to inform the formulation of recommendations
c. Use cost-effectiveness analyses, that are available or is known to the guideline panel (i.e., there is not a cost-effectiveness systematic review)
d. Do not routinely use cost-effectiveness evidence, rather, you use evidence about costs of the interventions in the context, to inform the recommendations development
e. Do not consider costs when developing recommendations

f. None of the above; Please explain _____

11. **Do members of the government/ministry participate in any one or more of the following steps/processes in the CPG development?** *(please mark all the possible options)*

a. Prioritization and selection of the guideline topic
b. Guideline scope definition
c. Questions definition
d. Literature review (search, selection, and assessment of the evidence)
e. Recommendation development (expert panel)
f. External review or feedback
g. Activities related to the implementation of the recommendations
h. Government members do not participate at all in any of the guidelines' development steps
i. Other: Please specify_____

12. CPG dissemination and implementation activities in which government may participate include (check all that apply):

a. Publication of guidelines in print or on a web site.
b. Quality assurance and monitoring (e.g. using quality indicators associated with guidelines to measure guideline concordance).
c. Funding decisions (e.g. reports or summaries for funding for drugs or technologies, human resource funding, funding related to system redesign).
d. Accreditation
e. Performance management and incentives (e.g., pay-for performance).
f. Other

g. Members of government do not participate in CPG dissemination or implementation activities.

13. In addition to inform clinical decisions, for what of the following purposes do the CPGs from your organization may be or are used in your context or country?

(Please check all that apply):

a. Quality improvement projects and activities at a clinic, hospital or region.
b. Benchmarking and setting clinical performance standards or system standards for a jurisdiction
c. Monitoring and reporting of quality (e.g. development and monitoring of quality indicators).
d. Coverage or reimbursement decisions (i.e., decisions about what drug, technology, or test, should be funded in a benefit/health plan or what should be reimbursed, at a national or provincial level)
e. Performance management incentives (i.e. tying salaries or hospital funding to performance outcomes (e.g., infection rates, operation rats, perioperative bleeding, etc.).
f. Hospitals' accreditation activities
g. Identifying research gaps (e.g., by research funding agencies, which evaluate gaps in CPGs to take decisions on research funding allocation for future projects/grants)
h. Medical or health professions education activities (i.e., CPGs are part of curricula in medical schools or are used to teach medical students or residents training on the best evidence-based practices, or to design tests/examinations)
i. Continuing medical education-CME- (i.e., CPGs or recommendations are tools to developing CME programs/activities)
j. Licensing or maintenance certification activities (e.g., board certification of medical specialties)
k. Judicial decisions (e.g., malpractice litigations as exculpatory [used by defendants] or inculpatory tools [used by plaintiffs])
l. Not used at all for any of the previous purposes (i.e., only for decisions at the clinical encounter)
m. Do not know/not sure_____

n. Other specific roles of CPGS that you may be aware of in your context/country?

- Please specify activity/process 1_____
- Please specify activity/process 2_____
- Please specify activity/process 3_____
- Please specify activity/process 4_____
- Please specify activity/process 5_____

Any additional comments? _____

14. **Is one of the aims or objectives of the CPGs your organization produce to inform or support one or more of the following activities?**

(Please Mark: Yes or No, in each of the activities)

a. Quality improvement projects: Yes__ No__ Sometimes __ Please explain: ____
b. Benchmarking or setting clinical performance or system standards: Yes__ No__ Sometimes __ Please explain: ____
c. Monitoring and reporting of quality (e.g. development quality indicators). Yes__ No_ Sometimes __ Please explain: _
d. Coverage, reimbursement or drug funding decisions Yes__ No__ Sometimes __ Please explain: ___
e. Performance management incentives (i.e. pay for performance): Yes__ No__ Sometimes __ Please explain: ____
f. Hospitals' accreditation activities Yes__ No__ Sometimes __ Please explain: ____
g. Identifying research gaps supporting research priority setting: Yes__ No__ Sometimes __ Please explain: ____
h. Supporting medical or health professionals' education activities Yes__ No__ Sometimes __ Please explain: ____

i. Supporting or informing continuing medical education (CME) activities Yes__ No__ Sometimes __ Please explain: _

j. Licensing, maintenance or board certification activities Yes__ No__ Sometimes __ Please explain: _

k. Judicial decisions (medical litigations) Yes__ No__ Sometimes __ Please explain: ____

l. Do not know/not sure_____

m. Other specific activities not mentioned above Yes__ No__ Sometimes __ Please explain: ____

- Please specify activity/process 1_____
- Please specify activity/process 2_____
- Please specify activity/process 3_____
- Please specify activity/process 4_____
- Please specify activity/process 5_____

If you marked sometimes in any of the previous, please under which circumstances that role may be

Any additional comments? _____

15. Are the teams, organizations or institutions in your context/country in charge of the following activities considered as <u>target users</u> of the guidelines' recommendations that you produce?

(*Mark: Yes or No, in each of the activities)*

a. Quality improvement projects: Yes__ No__ Sometimes __ Please explain: ____

b. Benchmarking or setting clinical performance or system standards: Yes__ No__ Sometimes _ Please explain: _

c. Monitoring and reporting of quality (e.g. development quality indicators).Yes_ No__ Sometimes_ Please explain:

d. Coverage or reimbursement decisions (drug funding decisions) Yes__ No__ Sometimes __ Please explain: __

e. Performance management incentives (i.e. pay for performance): Yes__ No__ Sometimes __ Please explain: _

f. Identifying research gaps supporting research priority setting: Yes__ No__ Sometimes __ Please explain: ___

g. Supporting medical or health professionals' education activities Yes__ No__ Sometimes __ Please explain: __

h. Supporting or informing continuing medical education (CME) activities Yes__ No__ Sometimes __ Please explain:

i. Licensing, maintenance or board certification activities Yes__ No__ Sometimes __ Please explain: ____

j. Judicial decisions (medical litigations) Yes__ No__ Sometimes __ Please explain: ____

k. Do not know/not sure_____

l. Other specific activities not mentioned above Yes___ No___

- Please specify activity/process 1_____
- Please specify activity/process 2_____
- Please specify activity/process 3_____
- Please specify activity/process 4_____
- Please specify activity/process 5_____

Any additional comments? _____

Appendix 2. Full list of organizations that participated in the survey

Accreditation Association for Ambulatory Health Care (AAAHC)	United States
Agency for Quality in Germany (AQuMed)	Germany
American Academy of Neurology	United States
American Cancer Society	United States
American College of Cardiology	United States
American College of Obstetricians and Gynecologists	United States
American College of Physicians	United States
American Physical Therapy Association	United States
American Psychological Association	United States
American Society of Clinical Oncology (ASCO)	United States
Belgian Health Care Knowledge Centre	Belgium
Berlin Chamber of Physicians/German Medical Association	Germany
Brazilian Medical Association	Brazil
Canadian Task Force on Preventive Health Care	Canada
Canadian Thoracic Society	Canada
Center for Clinical Practice Guideline Development / Evaluation at Children's Hospital of Fudan University	China
Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)	Mexico
Chair of Evidence-based healthcare and knowledge translation in Collaboration with the Quality Development Department, King Khalid University Hospital	Saudi Arabia
Clinical Practice Guidelines Unit, Malaysian Health Technology Assessment Section, Ministry of Health	Malaysia
College of American Pathologists	United States
Congress of Neurological Surgeons	United States
CONITEC - National Committee for Health Technology Incorporation	Brazil
Conseil Scientifique du domaine de la santé	Luxembourg
Czech Health Research Council	Czech Republic
Department of Health	Ireland
Dutch Association of Clinical Geriatrics (Nederlandse Vereniging Klinische Geriatrie; NVKG)	Netherlands
Dutch College of General Practitioners (NHG)	Netherlands
Dutch National Health Care Institute (Zorginstituut Nederland)	Netherlands

Dutch Nurses Association (verpleegkundigen en verzorgenden Nederland)	Netherlands
Dutch society of surgery	Netherland
Eastern Association for the Surgery of Trauma	United States
Effective Basic Services (eBASE) Africa	Cameroon
Endocrine Society	United States
European Academy of Neurology	International
European Association for Endoscopic Surgery	Netherlands
European Board of Cardiovascular Perfusion	Belgium
European Federation of the International Society for Digestive Surgery (EFISDS)	Netherlands
European Pancreatic Club	Germany
European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	Switzerland
Faculty of Medicine - Alexandria University	Egypt
FYMCA Medical ltd	United Kingdom
Instituto Nacional de Salud	Peru
Istituto del Pancreas - Verona	Italy
Japan Council for Quality Health Care	Japan
Joanna Briggs Institute	Australia
Kaiser Permanente Care Management Institute	United States
King Saud University Medical City, College of Medicine, King Saud University	Saudi Arabia
Korean Academy of Medical Sciences (KAMS)	South Korea
Ministerio de Salud de Chile	Chile
National & gulf center for Evidence based health care, at King Saud University for health science	Saudi Arabia
National authority for assessment and accreditation in healthcare (INEAS)	Tunisia
National Blood Authority	Australia
National Board of Health and Welfare	Sweden
National Health & Medical Research Council	Australia
National Heart Foundation of Australia	Australia
National Resource Fund (FNR)	Uruguay
Nederlandse Vereniging voor Medische Microbiologie. (Dutch Society for Medical Microbiology)	Netherlands
Osteba, Basque Office for HTA. Ministry for Health. Basque Government	Spain
Pan American Health Organization	United States
Peking University Health Science Center for Evidence-based Nursing	China

Prince Edward Island (PEI) Health and Wellness	Canada
Registered Nurses Association of Ontario (RNAO)	Canada
Royal Dutch Society for Physical Therapy	Netherlands
Scientific Advice Unit (Avalia-t). Galician Agency for Health Knowledge Management (ACIS). Galician Health Service.	Spain
State Expert Center of the Ministry of Health of Ukraine	Ukraine
Tehran University of Medical Sciences	Iran
The Center for Healthcare Quality Assessment and Control of the Ministry of Health of the Russian Federation	Russia
The General Authority for Healthcare Accreditation and Regulation	Egypt
The Norwegian Directorate of Health	Norway
The Society of Obstetricians and Gynaecologists of Canada	Canada
The WHO Regional Office for the Eastern Mediterranean (WHO/EMRO)	Egypt
Think Pink: Bahrain Breast Cancer Society	Bahrain
University of Medical Sciences	Iran
University of South Australia	Australia
US Centers for Disease Control (CDC.gov)	United States
Working Group Development of Guidelines Primary Care (WOREL)	Belgium
Working Group Development of Primary Care Guidelines	Belgium
World Health Organization Office (Afghanistan)	Afghanistan

Appendix 3: Additional reported roles and quotes from organizations:

"integration in computer systems"

"Development of decision aids"

"patients' information/education on public websites"

"implementation activities"

"inform disease management programs, organize coordination of care between sectors

"Supporting clinical decision making by individual nurses"

"enhancing quality of nursing profession (as additional activity of quality improvement within organisations"

"To support consumers to make informed decisions about their pathway during their breast cancer journey and to also educate those professionals to better direct their patient/s"

"Empowering patients around their disease"

"To inform evidence-based practice in psychology"

CHAPTER 4. CLINICAL PRACTICE GUIDELINES' ROLE IN DRUG FUNDING DECISIONS IN ONTARIO (CANADA) AND COLOMBIA: A MULTIPLE CASE STUDY

Chapter 4. Clinical practice guidelines' role in drug funding decisions in Ontario (Canada) and Colombia: a multiple case study

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Abstract

Background: Clinical practice guidelines (CPGs) are used to inform drug-funding decisions, one of its main roles outside the clinical encounter. However, the specific role of CPGs in this context and the extent and frequency to which they are used to inform these decisions is unclear. We aimed to understand whether CPGs have been used, how are they used, and under what conditions they are used in decisions about drug funding in two contexts, Colombia and Canada/Ontario.

Methods: A multiple-case study design was conducted. In Colombia, our case was focused in any drug funding decision, while in Canada it was limited to the cancer drugs. We interviewed key informants and we analyzed relevant documents. To respond to our question about "how?", we categorized the CPG uses as instrumental, conceptual and symbolic, and we used the country-level KT models' framework. To respond, "under what conditions?" we used the 3-Is framework. We applied the analytic technique of explanation building to understand the factors that have influenced the use of CPGs.

Results: We interviewed 18 key informants and reviewed 148 documents. We identified that CPGs had a major role in informing drug funding decisions in Colombia, while in Canada/Ontario, this role was minor. In Colombia, CPGs had instrumental (i.e. as an evidence source and for prioritizing drugs to evaluate), conceptual (i.e., to inform drug reviews document) and symbolic uses (i.e., as a rationale for decisions). Policy legacies (requirement for updating benefit package, creation of a methodological guide, and the heath technology assessment agency), political interests (CPGs as a cost-containment tool), and knowledge and beliefs (CPGs as a source of evidence) help to explain their instrumental use. In Canada/Ontario, the government structure (drug funding recommendations conducted at a federal level), the knowledge and beliefs (CPGs as tools to provide clinical context versus sources of evidence), explain that CPGs use was only conceptual.

Conclusion: Our results suggest that the use of CPGs in drug funding decisions was instrumental in the Colombian case, and very limited (Conceptual) in the Canada/Ontario case. Policy legacies, political

interests and ideas about the CPGs explain this major role in Colombia, while the government structure and different ideas on CPGs explain the limited role in Canada.

Background

One of the most challenging decisions in health care systems are those related to the funding of care options such as drugs. The complexity of these decisions has increased with the time given the increase in drug prices (with little growth in budgets), the speed with which new drugs and technologies become available, and the growing public pressures to fund new options as they become available (1). Payers usually make drug funding decisions by considering the value for money that a new drug provides. In many countries, these decisions are usually supported by health technology assessments (HTA), which are evidence-based documents that include effectiveness, cost-effectiveness and budget impact analyses, that inform decisions at the health care system level (2-4).

In contrast to a health systems-level perspective of HTAs, clinical practice guidelines (CPGs) are evidence-based documents that have typically focused on informing decisions made within the clinical encounter context (5, 6). However, CPGs have been increasingly used by other stakeholders, including those responsible for drug funding decisions (7). High-quality CPGs use the best available evidence to determine the clinical effectiveness of drugs, assessments of the drugs' benefits and harms, consideration of their implementability (i.e., availability and acceptability by clinicians and patients), and an analysis of resources implications of recommending a specific option (8).

HTA and CPGs differ in several aspects. CPGs are designed to respond to clinical questions, while HTA to policy-level questions. CPGs are typically broad as their target is a disease or a clinical scenario. In contrast, HTAs typically focus on one or a few interventions. Also, CPGs are increasingly systematically considering additional factors other than effectiveness and safety evidence, such as patients' values, use of resources, and implementability. CPGs typically have a larger social engagement process to their

development with respect to the composition of the development group and external review processes of draft documents. As a consequence, CPGs are very time consuming, while HTAs are developed in shorter times. Lastly, HTA have strong economic analyses, while costs considerations are commonly absent or, if present, they are not key elements of CPGs development.

Despite their differences, both share common grounds: they provide recommendations that are supported by the evidence, and sometimes a CPG and an HTA may use the same evidence to inform the recommendations of each. Thus, CPGs inform or can even facilitate the HTA process by providing evidence that is already available and synthesized, which might avoid duplication of efforts and can also provide an input with a clinical perspective. Some models have put CPGs in the center of the link between the effectiveness and the cost-effectiveness evidence and can inform the drug funding process(9).

In a recent critical interpretive synthesis, we found that the role of CPGs in influencing or informing economic decisions (such as drug funding decisions) is one of their main roles outside the clinical encounter (10). Moreover, in a recent international survey of CPG developers, we found that almost half of the organizations reported that their recommendations are used to support coverage decisions (11). Despite their potential, the role of CPGs outside the clinical encounter, and specifically in drug funding decisions, is poorly studied. There are little data on how the role is operationalized and under what conditions. This is a critical gap to address. Understanding this role may provide insights on how to develop better and implement CPGs to optimize their impact in this context. For example, presenting evidence in a manner more appropriate for policy stakeholders than for clinicians, or formatting recommendations that more may easily support funding decisions and their implementation. However, as a first step, it is important to understand the role of CPGs in a drug funding context. To this end, the aims of this study were to understand whether CPGs have played a role in drug funding decisions, how CPGs have played this role and under what conditions CPGs have been used in this role. These questions were explored by considering the cases in two settings, Colombia and Canada/Ontario.

Methods

The study applies a descriptive multiple case study approach guided by Yin's proposal (12). A set of questions was developed to guide the interviews and data collection for this study:

- Have CPGs played a role in drug funding decisions?
- How are CPGs used in drug funding decisions?
- Under what conditions CPGs have been used for this role?

The cases

The cases are defined as the role of CPGs in drug funding decisions in jurisdictions that reflect to governance styles and different CPGs production model. Jurisdiction one is labelled Colombia. It takes a solely national governance approach to drug funding, as will be described below. Jurisdiction two is labelled Canada/Ontario. This case reflects a governance in which both national (Canada) and provincial (Ontario) actors and systems contribute to ultimate access to drugs.

Colombia had a health system benefits' package, the Mandatory Health Plan (in Spanish: POS) which included a list of funded drugs and diagnostic tests available for all the citizens. Colombia started national production of CPGs in 2011 by a collaboration between the Ministry of Health (MoH), universities, professional societies and the Colombian HTA agency (IETS). From 2013, the CPGs helped to inform the 'evidence reports' developed to update the options available in the POS. CPGs active production existed until 2016. We studied the role of the Colombian CPGs in the decisions take during the period of active production (2011-2016) with an emphasis on the largest POS update that occurred in 2013.

In Canada/Ontario, our case was restricted to the cancer drug funding decisions. This scope was chosen because cancer drug funding decisions have a very unique, specific, and separated process from the rest of drugs with an unusual and interesting history of provincial and national participation. In addition, in Canada, there is not a national CPGs program that covers all the topics that may be of interest for drug funding decisions. The Canadian Agency for Drugs and Technologies in Health (CADTH), a Canadian

national entity, performs effectiveness and cost-effectiveness assessments of drugs, and provides recommendations on which drug to fund. The Common Drugs Review is body responsible for providing national-level recommendation on general drugs, while the Pan-Canadian Oncology Review (pCODR) provides national-level recommendations for cancer drugs. The latter were originally framed as non-mandatory recommendations by which any provincial MoHs had a choice to adhere and fund the drug, or not (13). However, it has been described that provinces typically adhere to pCODR recommendations in almost all the cases(14). Thus, while individual provinces have ultimate authority to determine which cancer drugs to fund, the evidence suggests that the final funding decisions by all provinces typically aligns with the recommendations that emerge from the national body.

The only national level government-supported CPGs program in Canada is the Canadian Task Force for Preventive Health Care. But their CPGs scope is on supporting primary care providers, and therefore, their recommendations rarely inform drug-funding decisions. There are some provincial-level government supported CPGs programs, typically in the field of cancer. For example, the Cancer Care Ontario's Program in Evidence-based Care (PEBC), has been producing CPGs for decades for Ontario (15, 16). In Ontario, PEBC's CPGs were used by Ontario leaders as an input into the cancer drug funding decisions when these decisions were provincially based. The PEBC eventually served as the source of CPGs during early iterations before the partnership between pCODR and CADTH was established. Thus, PEBC's CPGs have a history of being used to inform national cancer drug funding recommendations. The shift to CADTH enabled multi-provincial representation in the development of the evidence sources through a national team of pCODR. Moreover, the costs of CPG development moved from solely the responsibility of Ontario to a shared national arrangement managed by CADTH and pCODR. We studied the role of CPGs (evaluating the role of PEBCs CPGs and other CPGs) in the provincial funding decisions and the influence of the federal process on them, from 2011 to 2019.

Key Informants.

To maximize the selection process and create information-rich cases, purposeful sampling and respondent-driven approaches were used to recruit interview participants involved in funding decisions(17, 18). A list of potential participants, known to be involved in CPG development or in drug funding decisions processes was developed by the researchers' team. These participants suggested additional names of potential participants. A full list of participants was made with administrative leaders, government officials, methodological experts and other high-level stakeholders that have been part of the drug funding decision process or CPG development in CCO, PEBC, pCODR and/or CADTH (Canada), and in IETS, university developers and the MoH (Colombia).

Participants were initially categorized in three groups, each group focused on a different process: synthesis, prioritization, and decision. The *synthesis group (SY)*was comprised of individuals who are part of actual CPG production or evidence synthesis for drug reviews processes. These individuals typically contributed to CPG development, dissemination, and/or implementation or the preparation of evidence summaries for decision-makers. The *prioritization group* (PR) was comprised of individuals who were in charge of selecting drugs to be evaluated or coordinating the review analyses processes carried about by members of the synthesis group. The *decision-making group (DM)* was comprised of individuals who are part of decision committees, or participate in discussions, deliberations and/or final funding recommendation or funding decision. We expected, and we found, some overlap in membership and scope of roles between these categories. In Colombia, we interviewed participants from the national level, while in Canada/Ontario, from both the federal and the provincial level.

Candidate interviewees were invited to participate through recruitment emails (Appendix 1). Upon signed consent (Appendix 2), interviews were conducted face-to-face or via Skype® (Microsoft®), in English (Canada) or Spanish (Colombia) guided by the interview protocol (Appendix 3). Interviews lasted between 35-50 minutes. Two pilot interviews (one in each country) were taken to test the interview form. Interviews were audiotaped and transcribed verbatim. Written transcriptions along with memos were taken

throughout the interviews were used for the analyses. All the interview transcriptions, documents and memos (.pdf and .txt files), were exported to the NVivo12 software for Mac (QSR International, Cambridge, MA, US) for the analyses. Data collection continued until saturation of categories was reached.

Documents.

The documents considered included those that described evidence reports or CPG development methodology or discussed drug funding decision making, or policy documents related to these decisions. We reviewed methodological manuals, archival records, organizations' websites, media, evidence drug reviews, and published literature referred by interview participants and identified through focused searches on organizational web sites.

Analysis

Data were examined through an open coding process. Preliminary categories that emerged from the transcriptions, memos and documents were used to aggregate the data. Categories that were similar theoretically or connected in meaning were grouped in themes. We did categorical aggregation in final themes(19). Relevant documents and reports were also systematically tabulated and analysed against the emerging themes and data was triangulated with the interviews' findings (20).

Our dependant variable was the use or not of CPGs to inform drug funding decisions. To respond our research questions, the following approaches and considerations were used. Our first question was, *have CPGs played a role to inform drug funding decisions?* For this question we explored whether CPGs have been used and perceptions of decision makers if the role was significant or not.

How have CPGs been used? Two approaches were used to answer this question. First, we used the classification of research use scheme, which classifies the use as instrumental, conceptual or symbolic (21). Instrumental use involves the application of research in specific and direct ways; conceptual use occurs when research results are used for general enlightenment, i.e., results may influence decisions but in a more indirect way, and less specifically than in instrumental use. Symbolic use involves the use of research

funding to legitimate and sustain predetermined positions (21, 22). Second, we applied the knowledge translation (KT) framework (country model for linking research into practice) from Lavis et al. (23). This framework classifies how the knowledge moves at a country-level. It defines three models: 1) "push" model, which includes the scenarios in which the new recommendations from guideline developers are directed to decision-makers with the aim of influencing their use in the decision-making process; 2) "pull" model, where decision-makers seek CPGs and recommendations to inform their decisions; and 3) 'exchange and integrated' model, in which both evidence synthesis experts or CPG developers work together through a partnership.

Under what conditions have CPGs been used? To respond this question the "3-Is" framework was used to inform the main themes development (24). We used the framework to explain our dependant variable, i.e., the use of CPGs in each jurisdiction. This framework identifies three categories of influence on policy and decisions: ideas, interests and institutions. The "ideas" refers to the influence of knowledge and beliefs, and the values (i.e., the views of what "ought to be"); the "interests" category covers the influence of different interest groups; and lastly, the "institutions" category considers the influence of government structures, policy legacies and policy networks. This project was reviewed and approved by the Hamilton Integrated Research Ethics Board (HiREB), from McMaster University (project number #7244, Aug 29th, 2019).

Results

We invited 29 individuals to participate, from both countries, 15 from Canada and 14 from Colombia. A total of 18 interviews were completed (10 from Canada, eight from Colombia) (see Table 1). Eleven individuals were invited but did not participate (seven from Colombia and four from Canada) for the following reasons: scheduling conflict (four), did not reply to our invitation (five), and two declined. Table 1 summarizes characteristics of participants. The participants were key informants that have participated in components of drug funding in their respective jurisdictions and CPG development, and fit into the synthesis, prioritization, and or decision groups. Therefore, we considered that they provided rich data for our analyses.

Five, three, and two of the Colombian interviewees were classified into the synthesis (SY), prioritization (PR), and decision-making (DM) groups, respectively. One participant fitted into two groups, PR and DM. For the purposes of the study, this participant was asked to take on the perspective of a decision-maker only. Three, five, and two participants from Canada were categorized into the SY, PR, and DM groups, respectively.

In the Colombian case, a total of 56 documents were reviewed: newspaper articles (n=3); published primary studies (n=4);, methodological CPGs and manuals (n=5); policy analysis (n=1), laws and sentences (n=4) and evidence review reports (n=43). For the Canadian Case, 72 documents were reviewed: news releases (n=1); journal article or abstracts (n=5); technical report (n=2); methodological CPGs and manuals (n=4); and clinical and economic guidance reports (n=60). Below, we described each case, starting with a context of the study in each country.

The Colombian Case

Study context

Table 2 shows a timeline that describes events that influenced the role in drug funding decisions in Colombia. In summary, the POS (1993) defined what drugs were to be funded by the health care system (25, 26). The POS had not been updated for almost two decades until in 2008 when the Constitutional Court's Sentence T-760 compelled the MoH to update it (27, 28). At that time, the Colombian health care system was under a financial crisis, and one of the facilitators of this crisis was the increase in the health care expenditure related to drug costs. Between 2011 and 2012, in response to both the Sentence and the need for controlling the expenditure, two outcomes emerged: The *Methodological Guideline (MG) for Developing CPGs* document and the creation of the IETS, the national HTA agency. The MG provided guidance for developing GAIs (In English: Comprehensive Care Guidelines), which were composed of CPGs, cost-

effectiveness analyses (CEA), and budget impact analysis (BIA). The MG explicitly stated that one of the roles of the GAIs (CPG plus CEA plus BIA) were to inform drug funding decision-making

> *"Due to the aforementioned order of Sentence T760, this Methodological Guideline becomes more relevant since it will be useful for the contents of the POS to be updated in accordance with the best scientific evidence, based on a serious and well-conducted economic evaluation that allows, also, to define the impact that the intervention or treatment has on the value of the UPC"* (*excerpt from the MG)

In a second, updated, version of the MG (2013) the definition and content of GAIs were changed to "CPGs with CEA". The BIA was no longer part of its scope. Also, the updated MG no longer made reference to the GAI role to inform updates of the POS and drug funding decisions. Instead, the focus was that the CPG portions were to be used to inform clinical care decisions.

Following the release of the MG guidance in 2011, CPGs started to be developed by universities, a process that IETS began coordinating in 2012. Additionally, during 2013, the IETS evaluated 70 health technologies (57 drugs). These evidence reviews were used by a committee within the MoH that was in charge of the funding decisions. Thus, as of 2013, both CPGs and HTAs were used. Starting in 2015 (fully implemented in 2018), Statutory Law #1751 eliminated the POS. Instead of using GAIs to inform what care options would be funded for the population, all the available and prescribed interventions by physicians were going to be covered. Thus, the need for evaluating interventions to be included in the POS disappeared. Since 2018, a new process of exclusion analyses has been implemented. With this process, drugs are evaluated to define whether they will be excluded or will continue to be covered in the country's formulary. This evaluation follows an expedite literature review process that is not a complete HTA and goes through a stakeholders' deliberation and participation process. CPGs are no longer used to inform this process and the production of new or updates of existing Colombian CPGs has stopped since 2017. Currently, there are special drug reviews aiming to decide what to exclude from the formulary, that follows some explicit criteria, and CPGs are not part of these criteria. Our analysis is focused on the role of CPGs during the period of active CPGs production (2012-2016), and during which the largest POS update was performed (2013).

Have CPGs have played a role in drug funding decisions?

We found that CPGs were indeed used to inform the drug funding decision-making process. This role was considered major because CPGs' recommendations informed the final decisions during the largest POS update in 2013.

How are CPGs used in drug funding decisions?

Instrumental, conceptual and symbolic use analysis: The data shows that CPGs had instrumental, conceptual and symbolic uses. The *instrumental use* occurred as a prioritization tool and as a direct evidence source. As the former, recommendations of interventions were identified as priorities for drug evidence review and to contribute to the POS update. As the latter, with the aim of avoiding duplication efforts, when a Colombian CPG that covered the topic related to a drug of interest was available, a new full evidence review was not initiated. Rather, the CPG recommendation (either in favour or against), and the evidence base underpinning them, were used to develop a short evidence report. These reports that included the CPG alone with cost considerations informed deliberations and decisions. Of the 43 reviews used in the POS update, 17 (39.5%) were based on existing CPGs, and the remaining 26 (60.5%) were based on new full original evidence reviews for drugs that had not been covered by the available CPGs (Appendix 4). CPGs, authored within Colombia, had an instrumental use.

A *conceptual use* occurred in the analysis of drugs that were not covered by the available Colombian CPGs. In these cases, international CPGs informed the background or the discussion sections of the evidence reviews. CPGs were cited to describe aspects of the disease, for supporting the conclusions, or they supported the definition of the best populations and comparisons to consider in the analysis (PICO questions). Out of the 26 full evidence reviews for which there was not an already available Colombian CPGs, 17 of them (65%) explicitly stated that they used international CPGs to design their questions and/or cited international CPGs in their reports (Appendix 4). However, in these cases, neither the full evidence base nor the recommendations from the international CPG were used in an instrumental fashion. Lastly, a *symbolic* use was reported when a negative drug funding recommendation was aligned with international

CPGs recommendations (i.e., it was not recommended by CPGs) for a specific disease. Decision-makers use the CPGs as a 'back-up' in the discussions with different stakeholders.

KT Model Analysis: CPGs have been used following the *'pull'* model. Specifically, they are used as a "one-stop shopping" where decision-makers gather, or *'pull'*, the evidence they need, and use these data for drug funding decisions. The *'push'* model was less visible but also existed. CPGs recommendations were a criterion for prioritization of drugs to be evaluated. Therefore, when a Colombian CPG recommended any drug, this was a *'push'* for prioritizing it to be evaluated, and eventually to be funded. We did not find any scenario where the integrated or exchange model was applied.

Under what conditions CPGs have been used for this role?

The conditions under which CPGs have been used for drug funding decisions (Dependant variable) can be found in Table 3 categorized under the 3-Is framework.

Institutions: Government structures influenced the role of CPGs. Colombia has a centralized government, and drug funding decisions occur at one single level, and they are implemented throughout the country. Also, we identified some policy legacies and networks that influenced this role. The requirement of a benefits packages update (Sentence T-760), the development of the MG as one of the actions to control health care expenditure, the creation of the IETS, and the availability of a publicly funded CPG program directly influenced the use of CPGs.

Interests: In the analysis of the political interests, we found two time periods driven by two different government positions which influenced either in favour or against the use the CPGs. During the first period (2000-2009), the government, on the right side of the democratic spectrum, declared a state of Social Emergency to address a financial crisis. At this time, CPGs were considered as restrictive or cost-containment tools, rather than tools to facilitate evidence-informed decisions or to contribute to an overall dialogue of appropriate care or quality care.

"… And it is that due to the financial crisis, there was the idea that the clinical practice guidelines could be used as a restrictive coverage mechanism, where it will be restricted its prescription only to those interventions recommended by the CPGs. That was somehow a government's confusion […] this had a harmful effect, and doctors in Colombia lost trust in the guidelines. That…later took a while to recover, because with that the Social Emergency Law…" (DM1)

In the second period (2010-2016), a new, more centrist government, was in power. CPGs were reframed and evidence-informed guidance was promoted. So, while influenced in favour of their use in both periods, the political interests and goals were vastly different. Indeed, we identified that academic and research groups, patients' groups and professional societies supported the use of CPGs but were against their use as a cost-containment tool.

"… it starts around 2009… there was confusion… the social emergency state was declared and later it fell down, also the re-election of President Uribe falled… who was a quite authoritarian and right-wing leader…and a new president arrives more political, more conciliatory, but with a more international vision and the Ministry starts talking about the use of evidence but not as a restrictive tool. Until more or less the end of 2010 or 2011, when the Law 1138 finally came out, which gives strength to the clinical practice CPGs and gives life to the IETS […] that is when Colombia becomes more rigorous and made the methods for CPGs and economic analyses… the use of GRADE and AGREE and all those methodological tools…" (DM1)

Ideas: We found that the evidence-based nature of CPGs, the use of CEA, and the fact that CPGs were developed by well-known research and academic groups were values in favour of the use of CPGs. Played against their use, the value of austerity influenced their use as a cost-containment tool during the first period. When considering knowledge and beliefs, the idea that CPGs are seen as a source of evidence (and of CEA in some cases), instead of the RCTs, definitely influenced in favour of their use. Against this role we found several limitations that were pointed out by participants: recommendations are not policy-relevant, require a considerable time for development, there is need for training decision-makers, the strength of the

recommendations is not very informative for decision-makers, conflicts of interests handling is inadequate in many CPGs, and the financial sustainability of a CPG program is challenging.

Canada/Ontario Case

Study context

Table 2 provides a timeline summary of the events that could have influenced the role of CPGs in this case. We were interested in the drug funding decision at the provincial level and the interaction with the federal level. However, as we will explain below, the drug funding process had a significant change in the last years with the creation of pCODR and the federal level became a major driver influencing the provincial decisions. Thus, both a national and a provincial lens were required to interrogate our case

Canada has a publicly funded health system in which the roles are divided between the federal and the provincial/territorial governments, with the latter the primary actor in how the health system is organized(29). pCODR is the federal initiative that through a participative process including government, patients, manufacturers and clinicians, assesses the cancer drugs that are to be eligible for public reimbursement and generates funding recommendations at a federal level(30). As the ultimate party responsible for funding, each province then has the option to accept the pCODR recommendation or not. However, since the pCODR process was established, in almost all cases, provinces are aligned with pCODR recommendations(14).

pCODR develops clinical guideline reports (CGR) and economic guidance reports (EGR). CGR is an evidence-based clinical report based on material provided by the drug manufacturer, studies identified through an independent systematic review conducted by a 'Methods Team' and input provided by the panel advisory group ('Clinical Guidance Panel'), and by patients' groups and clinicians. Although CGR is an evidence-based document that may cover most of the analyses that are covered by a CPG process regarding a drug's evidence, CGR are much narrower in scope. They have a very focused question on determining the

effectiveness and safety of the drug, they narratively describe the available RCTs (study design threshold used), the process is not as systematic, and they do not perform a statistical combination to summarize the results. The CGR, in contrast to high-quality CPGs, do not take the perspective of a clinical decision nor do they systematically assess the other factors such as patients' preferences, or implementability, nor goes to external review and it is not based on a multidisciplinary team. The EGR reviews and appraises the pharmacoeconomic information provided in the submission by manufacturers, with input from CGR and from registered patients' group and clinicians, and the 'Economic Guidance Panel' prepares it.

Both, the CGR and the EGR are used by pCODR Expert Review Committee (pERC), whose members deliberate and makes the final drug funding recommendations. pERC is composed of oncologists, health economists, an ethicist, pharmacists, and patient members. pERC decisions are usually one of three: negative (recommendation against funding the drug), positive (recommendation in favour of funding the drug) and conditional (a recommendation conditioned to the cost-effectiveness being improved to an acceptable level through successful negotiation with the drug producer)(31).

PEBC is the largest CPG producer in the country, accounting for one-fifth of the total number of Canadian CPGs(32). PEBC CPGs are aimed to inform clinical decisions at the Ontario level, but they have been used for decision making by other provinces and to inform national decisions. In the establishment of the pCODR process, elements of the PEBC model were used in designing the evidentiary review methods, and several stakeholders in the PEBC development processes also contributed to being part of the pCODR governance structure (33).

Have CPGs have played a role in drug funding decisions?

We found that, during the period of study (2012-2019), CPGs, neither PEBC's nor any other CPG, have not had a major role in drug funding decisions in Canada/Ontario. CPGs, however, had a minor role in informing background and discussion sections of the CGR and ECR and the PICO questions development in the pCODR process (see below).

How are CPGs used in drug funding decisions?

Instrumental, conceptual, and symbolic use analysis: CPGs were used in a *conceptual* way. CPGs were cited in the background section of CGR/EGR reports to describe the disease or were cited in the discussion section when analyzing the results. Also, in other cases, CPGs supported the definition of the populations, relevant comparisons, and to identify the most relevant outcomes to be measured. Often the PICO questions from the CPGs were used for these purposes. In an analysis of the CGR/EGR developed by pCODR between 2018 and 2019. Out of 60 reports, any CPG was mentioned in 21 of them (35%), primarily cited and discussed in the background section and less frequently (4/6.6%) in the feedback provided by manufacturers, sponsors or clinicians. Of the 21 reports in which CPGs were cited, only two reports mentioned PEBC CPGs the remaining were CPGs authored by international groups (appendix 5).

A *symbolic use* was also identified. When available CPGs aligned with the final CGR/ECR recommendation, it facilitated the discussion with stakeholders to defend their decision. Some participants consider that agreement with the CPG is both, "clinicians support" and a confirmation of what is, or what is not, or what should be, the standard of care.

> *"It's just that if the guidelines are available that's great. I can reference the guidelines so there's clinician support" (PR6)*

> *"So, if you accept the guideline as defining what the clinical standard of care should be then the guideline provides confirmation around the appropriateness of that intervention versus a specific just saying what the evidence says this but maybe all clinicians don't agree. But if you have a guideline it's gone through such a comprehensive process and provides a statement regarding the broader appropriateness of the therapy or intervention, that is… support…" (PR4)*

KT models: According to the country-level KT (23), in this Canada/Ontario case, although minor, we found a *'pull'* model. CPGs are searched and cited in the CGR/EGR, they inform the context of the disease and provide insights to the components of the CPGs' PICO questions. We did not find any scenario where the *'push'* or 'integrated or exchange' models were applied.

Under what conditions CPGs have been used for this role?

The summary of the conditions under which CPGs have had a conceptual (dependant variable) and not an instrumental use is detailed in Table 3 categorized under the 3-Is framework.

Institutions: Before 2011, cancer drug funding decisions landed squarely at the provincial level. However, this led to varying access to cancer drugs as a function of the jurisdiction in which patients lived. To create equal access and greater harmony across the provinces, the federal CADTH/PCODR strategy was put in place. Over time, the federal government played an increasingly major role, in the drug funding recommendations. As stated above, in almost all the cases the provinces accept CADTH/PCODR decision(14), ergo, the federal processes have been ultimately impacting final decisions. Furthermore, the CADTH's methodology has been built to respond to requests in a short time frame (180 days), which plays against the use of CPGs, which are commonly not available when there are drug reviews requests

Interests: We identified the interest of clinicians from the pERC in the idea of using more CPGs for drug funding decisions. Also, three participants (one DM, one PR and one SY participant) considered that CPGs development should be more aligned with drug funding decisions. From their point of view, this would make the process more efficient and will also take advantage of the input of very rigorous methodology that is used in, for instance, PEBC's CPGs development

Ideas: A key factor is the idea that, the source of evidence for drugs effectiveness is the RCT, not evidence synthesis or the CPGs. Although CPGs are based on the search and synthesis of RCTs, the synthesis, analysis, and interpretation of the RCTs evidence in many CPGs are not considered trustworthy by PR participants. The reasons reported are uncertainty in their systematic methods, and poor or no management of conflicts of interests. Additional identified limitations are that CPGs development is time consuming, they do not consider costs, and that trustworthy Canadian CPGs are not commonly available when a review is needed, while available international CPGs lack of Canadian context

"I think there's just so much missing information and that guidelines (..) that it makes it difficult for us to rely on it. Maybe, if we had more information like (..) kind of how they were developed… How valid are they in the current environment"? (PR4)

As a result, CPGs are perceived as clinicians' opinions rather than evidence-based documents and therefore they should not be a resource to inform the drug funding process.

Discussion

Principal findings

In our multiple case study, we provide a deep understanding of the role of CPGs in drug funding decision making in Colombia and in Canada/Ontario. In our analyses, we found that, indeed, CPGs had crucial participation in informing drug funding decisions in the Colombian context, but their most recent role in Canada/Ontario context has been minor during the study periods.

CPGs had *instrumental, conceptual and a symbolic* use in Colombia, and only *conceptual and symbolic* in Canada/Ontario. *Instrumental* uses were as a prioritization criterion for drug funding evaluation and as an evidence source. Indeed, Colombian CPGs provided all the information about the effectiveness and sometimes the cost-effectiveness, of a drug to be evaluated. In both cases, we found a *conceptual use* when CPGs informed the background and discussion sections of the evidence reviews and in providing context and the most relevant populations, comparisons and outcomes, to frame the evidence reviews. A *symbolic use* was found in both jurisdictions, with the CPGs providing additional rationale for the final negative recommendation for funding made by decision-makers.

As a KT tool, CPGs in Colombia were used as in both *'pull'* and *'push'* models, with the former the major driver. In contrast, in the Canada/Ontario context, although minor, only the *'pull'* model was found. The exchange and integrated models are considered the best KT models. In them, the knowledge producers

(CPGs developers) develop a partnership with decisionmakers to reduces duplication of efforts and allow efficient knowledge use and production(23). These models were absent in both cases.

The 3-Is framework was used to understand how CPGs informed drug funding. In Colombia, policy legacies had a major role in explaining the *instrumental use* they had: Constitutional Court's mandate to update the POS, the development of the MG which stated that CPGs had to inform the POS update, and the creation of the IETS. We found that the financial crisis of the Colombian health care system led the country into an intense circumstance in which CEA along with CPGs, were considered as one potential solution to control health care expenditure (34-36)

Among the political interests, we found that both governments in power during the studied period, a right-wing and a central-right wing government, had interests in CPGs, but for different reasons. The former, as a cost-containment-tool(37), and the latter, as an evidence-based tool. Interest groups, such as academic bodies, scientific associations and patients' organizations also had an interest in using CPGs to inform drug funding decisions, but not as a cost-containment tool. Lastly, a key factor in Colombia was the idea that CPGs, not the individual RCTs, were considered a source of evidence, and in some cases, of cost-effectiveness. Naturally, the CPGs are based on the systematic evaluation of the RCTs that assess drugs' effectiveness. However, in the Colombian case, the term "RCTs" was not brought up during the interviews by DM and PR, rather the analysis or the use of CPGs. The reasons for considering the CPGs as important sources of evidence might be related to the lower of technical capacity for achieving a deep understanding of the evidence-based process, until the MG and the IETS were launched.

CPGs can be pursued and designed to take on a perspective that aligns to a health systems' interests' context in addition to a clinical context or patient/public context(38). We consider that including de novo CEA in the CPGs development was a clear sign of the intention of using CPGs to inform drug funding decisions. However, it is not clear how in Colombia the CPGs became a major actor for drug funding decision, rather than just considering the creation of an HTA. The creation of the MG occurs in a period out

of the study focus, but one hypothesis might be an interest of decision-makers in both, informing drug funding decisions, and through clinical recommendations, in producing cost-containment.

Lastly, the *conceptual use* in Canada/Ontario appears to be attributable to government structures (i.e., the process at the federal level, by pCODR), and less to policy legacies. The idea that CPGs are perceived by participants from the PR group more as clinicians' opinions rather than an unbiased evidence source also compromised their value. Additionally, PR and DM participants identified several limitations that prevent CPGs from being used in these decisions. Factors such as poor conflicts of interest's handling, low quality of most of available CPGs, the fact that they are time-consuming, the lack of costs considerations, and lack of relevant Canadian CPGs were reported.

The disagreement between CPGs recommendations and a final drug-funding recommendation, although explained by decision-makers as a problem associated to low quality and lack of conflicts of interests' management, it may also be explained from an alternative angle. Even in the scenario of high-quality CPGs, these disagreements may result as a consequence of the perspective. CPGs usually take the lens of clinicians who threshold for benefit and desire to support their patients, which may not always align with that of a funder who must more explicitly be responsible for resources.

In summary, in Colombia, CPGs were considered as the status quo of evidence source, and this was supported in the high confidence decisionmakers had on the process. This approach has benefits and limitations. The availability of CPGs could reduce duplication efforts and prevent the development of new evidence documents, but at the same time using recommendations to inform drug funding decisions create the risk of supporting decisions on evidence of very-low quality, in some cases. In contrast, in Canada/Ontario, CPGs were seen as another evidence-based tool that had too much influence from clinicians with too much uncertainty on their process, which make them untrustworthy. Thus, decisionmakers would prefer to trust in their own evidence-based documents, i.e., CGR/EGR to inform their decisions.

Strengths and limitations

This case study has several strengths. To our knowledge, this is the first study that has specifically analyzed the factors that influenced the role of CPGs in drug funding decisions. Also, we analyzed two very different contexts which allowed us to have a broader picture of how CPGs might be used. Lastly, we interviewed key informants, and we evaluated different documents and evidence sources such as legal documents, journal articles, methodological manuals and a group of evidence reports, from both countries.

However, there are some limitations to describe. First, the differences between both cases may explain differences in the results. In Colombia, there was a national, one level process with a single CPGs' production that provided recommendations at a national level. In Canada/Ontario, the case was a mixed jurisdictional model. Namely, there are decisions made at the provincial level and also, recommendations from pCODR that are made at the federal level. Moreover, there is a lack of national CPG development, and we analyzed one provincial CPG producer. This complex scenario in the Canada/Ontario case is much more difficult to compare to the single, unique level in Colombia.

Additionally, in examining this setting, we focused on the national role and role of one province, Ontario. In this case, and compared to the past, while Ontario makes the final decisions about what cancer drugs to fund, it has abdicated the control of creating the sources of evidence used to make recommendations and inform these decisions to the national pCODR process. Whether the specific insights we gained in this dyad would be similar to those we might have gained if other provinces in Canada were studied or in jurisdictions that have similar national – provincial/state relationships are not known.

Findings in relation to other studies

We did not find any literature that has analyzed the role of CPGs in drug funding decisions. Nevertheless, several authors have highlighted how CPGs are good in supporting the health care rationing initiatives (39-42), while others have highlighted the need for using CPGs in conjunction with CEA to support coverage decisions (37, 40, 43-45). These findings were summarized in our recent critical

interpretive synthesis on the roles of CPGs outside the clinical encounter (10). Moreover, in our international survey of CPGs' developers, almost half of them reported CPGs are used in supporting coverage decisions. However, there is no specific literature on how this role occurs in different contexts.

Implications for research, policy and practice

Our findings are important for CPGs developers, researchers and policymakers. We have highlighted key methodological considerations that will be helpful for developers in cases where CPGs are to be considered for informing drug funding decisions. Also, researchers will benefit from these findings because we have highlighted areas that require more research. For instance, the relationship between HTA and CPG in different contexts requires further study. It is not clear what might be the best model of collaboration between both evidence-based documents.

Additionally, from the perspective of the CPGs development, it is clear that the concept of costs and resources use should be part of the discussions when developing recommendations for a policy purpose. However, does this then move to HTA territory? The methods for considering costs and the potential role of CEA in CPGs development are not entirely developed, and they are not free of limitations (46, 47). From the drug funding perspective, there are also some challenges and questions that arise if CPGs are to play a role in this context. Should CPGs recommendations inform the HTA processes or not, as a means to reduce duplications of efforts? If CPGs are to be used, would it be preferable to have recommendations that were developed informed by CEA methods? Alternatively, CPGs could focus on clinical recommendations and the CEA could be performed "post-publication" by another group. These are some questions that remain unanswered and require further research. The answers to these questions might be very contextually dependent, and our work provides interesting insights to this discussion. The GINAHTA (https://g-i-n.net/working-groups/ginahta/toolkit) initiative from the Guidelines International Network, for instance, aims to increase collaboration between CPGs and HTAs and thus, may benefit from our findings. Also, researchers interested in developing or improving CPGs methods might benefit as well, as they can create

tools or approaches that facilitate the use of CPGs in these decisions. Moreover, researchers may also consider studying the role of CPGs in other drug funding decisions contexts.

For policymakers, our findings will be useful as we have provided key insights, limitations and methodological considerations from two different countries that should be analyzed if CPGs are being considered for informing these decisions at a country level. For instance, policymakers that may be thinking about creating or modifying national CPGs programs, might find our results interesting to define the scope and the roles of CPGs in their drug funding decisions.

Conclusions

The role of CPGs in drug funding decisions was found major in the Colombian case and limited in the Canadian case. The *instrumental use* of CPGs in Colombia is explained mostly by policy legacies, due to specific government political positions and specific beliefs around evidence and CPGs, which ended up in introducing CEA in the CPG development to inform drug funding decisions. In Canada/Ontario, the role was very limited (*conceptual and symbolic use*, only) and CPGs only informed the writing of the drug evidence reports and supported the development of the review PICO questions. It is reasonable to think that the limited role in Canada might be the case in many other countries in which CEA are not part of the CPGs development.

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Table 1. Characteristics of the participants from both countries

Country	N (%)	Role groups	Acronyms	Affiliations
Colombia	8 (44%)	Decision makers (2)	DM1, DM2	Ministry of Health, *Instituto de Evaluación Tecnológica En Salud (Colombian HTA agency)* and others*
		Prioritizers (3)	PR1, PR2, PR3	
		Synthesizers (3)	SY1, SY2, SY3	
Canada	10 (56%)	Decisions makers (2)	DM3, DM4	Cancer Care Ontario, Canadian Agency for Drugs & Technologies in Health, Program in Evidence Based care, and Others*
		Prioritizers (5)	PR4, PR5, PR6, PR7, PR8	
		Synthesizers (3)	SY4, SY5, SY6	

*Affiliation of three participants is not provided to keep confidentiality (they are not part of these organizations but have been part of committees and it may be easy to identify them with their affiliation)

Table 2. Events linked to whether CPGs have an instrumental use in the drug funding decision processes in Colombia and Canada/Ontario

Year	Colombia	Canada/Ontario
1989	--	- Canada: CADTH was created under the name of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), known today as CADTH, by Canada's federal, provincial, and territorial governments to contribute to evidence-informed decision-making in Canada
1993	- Law 100 is enacted- This law had the aim of standardizing the access to health technologies and services across all insurers and providers, public and private(13). - Creation of a benefits' package comprised of drugs, medical devices, and diagnostic tests that would be funded by the health system, under a health care service called a 'mandatory health plan' (In Spanish, POS)(14).	--
1997	--	- Ontario: Cancer Care Ontario established (1995) and launched its PEBC program for the development of CPGs, housed at McMaster University - Ontario: between 1997 and 2011, the PEBC CPGs provided recommendations about drugs, which, in addition to economic analyses performed by CCO, Ontario's Ministry of Health and Long-Term Care (MOHLTC), where final policy decisions were made.
2007	--	- Canada: The Joint Oncology Drug Review (JODR) was created. This effort provided an interim drug review process in which evidence-based recommendations for cancer drugs were developed(15). Before this, provinces and territories had separate regional drug review processes to inform their local funding decisions
2008	- Sentence T-760 is handed down. It ordered a deep restructure of the health system, including among others, the need for a regular update of the POS(16, 17).	--
2011	- Law 1438 is enacted (Launched 2012). It created the HTA agency (In Spanish, IETS). The IETS produces evidence-based information to inform public policies and health care practices in the country through the coordination of both CPGs and HTA processes and supports the MoH in decision-making through the use of the best research evidence	- Canada: PCODR was created (created 2010, launched 2011) by the provincial and territorial Ministries of Health, excluding Quebec, to succeed the JODR. PCODR aim was to assess the clinical and cost-effectiveness information of new cancer drugs to bring consistency and clarity to the assessment of these drugs. - Provinces streamlined their drug funding processes and started adhering to the PCODR recommendations
2012	- Launching of the Methodological Guideline (MG*).* The MG provided recommendations for developing "comprehensive care CPGs" (in Spanish, *Guías de Atención Integral; GAI*), which were composed of three elements: CPG, cost-effectiveness analyses (CEA), and budget impact analysis (BIA).	--
2013-2014	- A second version of the MG was launched. GAI became "CPGs with economic analyses", and BIA was removed. CPGs were not explicitly developed for updating benefit package - IETS took over the CPGs' coordination.	--

	- IETS and MoH conducted the first large process to update the POS. The IETS evaluated 70 technologies through evidence reports that were used by the MoH for making these decisions.	
2015	- The statutory law is passed (Law 1751). It established that by default all the available interventions prescribed by physicians will be covered by the health system, unless they are part of an "exclusions list". Thus, this eliminated the POS, and the need for evaluating interventions to be covered and created a new process of exclusion analyses which has been implemented in 2016. Colombian CPGs are not playing a role om this process and CPGs have not been developed since 2017.	- Canada: PCODR is added to the CADTH structure.

The case of Colombia is focused on the period between 2011-2016, while the Canada/Ontario case is focused in the period between 2011-2019. Events depicted in the table are aiming to explain the roles of CPGs in these two different periods. The outcome of interest (Dependent variable) was whether CPGs have been sued or not in both jurisdictions. BIA: Budget Impact Analysis; CADTH: Canadian Agency for Drugs & Technologies in Health; CEA: Cost-effectiveness analyses; CPGs: Clinical Practice Guidelines; GAI: In Spanish: Guías de Atención Integral; these were documents that encompassed clinical practice CPGs, cost-effectiveness analyses and budget impact analyses; HTA: Health Technology Assessment; IETS: *Instituto de Evaluación Tecnológica En Salud* (Colombian HTA agency*);* JODR: Joint Oncology Drug Review; MG: Methodological CPG; MoH: Ministry of Health; PCODR: pan-Canadian Oncology Drug Review; POS: (in Spanish: *Plan Obligatorio de Salud)* Health Mandatory Plan, or the benefit package list

Table 3: Role of CPGS in drug funding decisions: Whether CPGs are used, and how and under what conditions they are?

Research questions			Colombia	Canada/Ontario
Have CPGs been used?			Yes; CPGs played a major role as a tool to update the benefits package which includes drug coverage (CPGs as source of evidence and also to inform background/discussion sections and PICO question (See below)	Limited; CPGs play a very minor role. CPGs are used in some specific moments playing very minor roles (informing background, discussion, and PICO questions- see below-).
How are CPGs used?			**- Instrumental use:** ▪ Prioritization tool (to define what interventions should be evaluated) ▪ Source of evidence (Evidence tables and recommendations from Colombian CPGs used to develop short evidence reports used to inform decisions, instead of full evidence, 'de novo', reviews). **- Conceptual use:** ▪ Informing the review background section (international CPGs are cited in background section of full evidence reports) ▪ Support the design of the review PICO question (international CPGs are used to inform the questions development in full evidence reports). **- Symbolic use:** ▪ CPGs may be brought up to the feedback provided by stakeholders (usually in requests for revisions when disagreement between international CPGs and report recommendation)	**- Instrumental use** *(no instrumental use was found)* **- Conceptual use:** ▪ Informing and supporting the review background section (international CPGs are cited in the background section of the evidence reports) ▪ Support in the design of the review PICO question (international CPGs are used to inform the PICO questions development in full evidence reports). **- Symbolic use:** ▪ CPG used as back-up in discussions with stakeholders when a negative drug funding recommendation aligned with existent CPGs
Under what conditions are CPGs used or not used? *(Application of the "3-Is" framework)*	**Institutions**	**Govt. structure**	Unitary centralized government with by one national Ministry of Health.	Federal government. Initially, each province had their own drug funding decision process. From 2011, PCODR provides a federal process. Provinces are still autonomous, but they follow PCODR recommendations in almost all the cases.
		Policy legacies	**- In favour of the major instrumental use** ▪ Requirement for a benefit package updating. There was a need for updating the POS as a mandate (Sentence T-760/2008) ▪ The development of the methodological guideline (MG). This was an action to control health care expenditure, which had skyrocketed and was leading the system to a financial crisis. It provided a roadmap to develop evidence-based CPGs and boosted a national CPGs program that increased the country's capacity in evidence synthesis and CPGs. ▪ The creation of the IETS (HTA Agency) by the Law 1438(2011). The law stated that decisions about the POS should be based on CPGs developed according to scientific evidence. This put research evidence in the center of the decision-making. ▪ The availability of a publicly funded CPGs' program. The MoH could trust in their own CPGs rather than professional societies' CPGs	**- In favour a conceptual use** *(Against having a major instrumental role, which did not happen)* ▪ The CADTH pCODR was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The aim was to homogenize the cancer drug funding process across the provinces. This played in favor of having a conceptual minor role, rather than a major instrumental role as it was in the past, when PEBC's CPGs were used to inform the drug funding process in Ontario. This case, (Ontario) was initially identified as a good scenario to understand the role of CPGs because this province has had their own CPG program for a quarter of century. This was not the case and PEBCs CPGs were no longer relevant for these decisions.

	Interests	**Political interests and Interests' groups**	**Political Interests** **- In favour of the instrumental use** ▪ The right-wing government (before 2009) was interested in using CPGs but as a tool for cost-containment. **- Against of the instrumental use** ▪ The center-right government in power 92009-2014) abandoned the idea of using CPG as a cost-containment tools. **Interests' groups** **- In favour of the instrumental use** ▪ Academics, patients' groups, and professional societies supported the idea of using CPGs for drug funding decisions **- Against of the instrumental use** ▪ Academics, patients' advocacy groups, and professional societies against the use of CPGs as a cost-containment tool	**Interests' groups** **- Against the conceptual use** *(in favour of an instrumental use)* ▪ Clinicians support the idea of using CPGs for drug funding decision-making ▪ Clinicians consider that CPGs development should be more aligned with drug funding decisions: A methodology to develop drug reviews and CPGs simultaneously, or in sequence, should be consider. ▪ Some experts acknowledge the utility of CPGs and consider that CADTH might in future consider the development of CPGs. However, if that is the case, the current process should be deeply restructured.
	Ideas	**Values**	**- In favour of the instrumental use** ▪ Evidence-based nature of the CPGs made users perceive them as trustful (CPGs were considered sources of evidence) ▪ Well-recognized research and academic groups being responsible of the CPGs	**- In favour of the conceptual use** *(in favour of an instrumental use)* ▪ Evidence-based. This value was considered in favour of a minor role due to the idea that "evidence-based" means for participants, based on the analyses of RCTs, not CPGs.
		Knowledge/beliefs	**- In favour of the instrumental use** ▪ CPGs are considered as a source of evidence, and in some cases a source of CEA. CPGs, and not the RCTs, considered an evidence source for drugs effectiveness. The lack of enough technical capacity might explain this idea among some decision-makers. **- Against a major instrumental use** ▪ CPGs have many limitations, such as: o Recommendations are clinically (not policy-) relevant o <u>CPGs require a considerable time for development</u> o There is need for training decision-makers in CPGs methods. o <u>Conflicts of interests handling is poor in many CPGs</u> o Financial sustainability of CPGs program is very challenging.	**- In favour of the conceptual use** *(in favour of an instrumental use)* ▪ The real source of evidence for drugs effectiveness are the RCTs, not CPGs. Most of CPGs are perceived as clinicians' opinions rather than evidence-based documents. ▪ Identified limitations of CPGs: o Low methodological quality (decision-makers commonly do not trust in their methods) o <u>Poor management of conflicts of interests (relationships clinicians/patients' organizations with industry)</u> o <u>CPGs are time-consuming</u> o Lack of availability of trustworthy Canadian CPGs o Available international CPGs without Canadian context o Almost all CPGs do not consider costs or CEA. ▪ CPGs are good tools to provide clinical context, prescription patterns, relevant population, comparators and outcomes.

<u>Underlined</u> are the factors found as commonalities between both cases.
Acronyms: BIA: Budget Impact analyses; CADTH: Canadian Agency for Drugs & Technologies in Health; CEA: Cost-effectiveness analyses; CPGs: Clinical Practice Guidelines; IETS: *Instituto de Evaluación Tecnológica En Salud* (Colombia HTA agency); MoH: Ministry of Health; MG: Methodological Guideline; N/A: Not applicable; PCODR: pan-Canadian Oncology Drug Review; RCTs: Randomized controlled trials.

Appendices

Appendix 1. Email's correspondence script

Date XX/XX/XXXX

Subject: Request to participate in the study: **"Clinical Practical Guidelines' role in Drug funding decisions in Canada and Colombia: A multiple case study."**

Dear participant,

I am writing to you because I am conducting a study about the **Clinical Practical Guidelines' role in Drug funding decisions in Canada and Colombia: A multiple case study**. You are being invited to participate in our research project. We are interested in understanding how and under what conditions CPGs are or were used by decision-makers when making decisions about drug funding. Your experiences, views and perceptions will be crucial to this project.

In the case that you accept this invitation, we have planned to develop an interview of 40-60 minutes of duration. By completing this interview, you consent to the anonymous data collected to be used for the research study and to be summarized in aggregate in publication.

If you consent to participate in the survey, please reply this email with your confirmation to Ivan D. Florez (florezid@mcmaster.ca). Hamilton Integrated Research Ethics Board in Hamilton, Ontario, Canada has reviewed this study, has approved this study. If you have any questions, please feel free to contact me: Ivan D. Florez (florezid@mcmaster.ca)

Thank you very much for your time and contribution.

Sincerely,

Ivan D. Florez

MD, MSc, PhD candidate

Health Research Methodology program

Department of Health Research Methods Evidence and Impact, McMaster University, Canada

Appendix 2. Informed Consent

LETTER OF INFORMATION / CONSENT

Clinical Practical Guidelines' role in Drug funding decisions in Canada and Colombia: A multiple case study

Investigators:

Local Principal Investigator:

Dr. Melissa Brouwers

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Department of Health Research Methods,

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Purpose of the Study

The purpose of this study is to understand how and under what conditions clinical practice guidelines (CPGs) are used by policy-makers when making decisions about drug funding. Clinical practice guidelines originally created to inform decisions at the clinical encounter level are also used in many other contexts. To date there is no literature that has analyzed how these guidelines are used and what roles they play in decision making in those contexts. One of the key contexts is the drug funding decisions, i.e., decisions about drug coverage (including universal and insurance coverage), and reimbursement decisions, at different levels of the health care systems. Understanding the roles of CPG in this scenario may be useful to guideline developers and guideline users to enhance their

development and their use and adoption. We, therefore, are conducting a study to understand how CPGS have been used in these types of decisions in a high-income (Canada) and in a middle-income country (Colombia)

You are being invited to participate in this research project because you have been identified as an individual who is expert in guideline development, implementation or use, or have participated in one of the steps of the process of drug funding decision-making in Canada or Colombia. You have been chosen because you have met one of the following criteria: (1) individuals who are part of CPG production or synthesis process (usually individuals who are part of the CPG development, dissemination, and/or implementation, or individuals who prepare health technology assessment reports, health systems guidance documents, policy briefs or summaries for decision-makers); (2) individuals who are or were in charge of prioritizing (or selecting technologies to be evaluated or assessed); or, (3) individuals who are or were part of decision committees, or participate or participated in discussions, deliberations and/or final funding decisions. Your input and experience are crucial to understand CPG roles, advantages and disadvantages. By completing this survey, you consent to the anonymized data collected to be used for the research study and to be summarized in aggregate in publication.

Procedures involved in the Research

After your acceptance to participate in this study, I will be asking you questions to obtain your views about your experience, views and perceptions on the topic. The interviews will be carried out face to face or by any application that specializes in providing video chat and voice calls (e.g. Skype, or Webex). The semi-structured interview is composed for approximately 15 questions (the number of questions may vary depending on which of the three groups that were described above, you may be classified. The study involves the audio taping of your interview. Tapes will be transcribed.

Potential Harms, Risks or Discomforts:

The risks involved in participating in this study are minimal. You do not need to answer questions that you do not want to answer or that make you feel uncomfortable. Any time during the interview you can stop to take a break. You can withdraw (stop taking part) at any time. I describe below the steps I am taking to protect your privacy.

Potential Benefits

The research will not benefit you directly, but it is aimed at learning about how and under what conditions CPGs are used for drug funding decision making. This will benefit you, and other individuals such as guideline developers, implementers and decision-makers in improving how CPGs are developed or used.

Confidentiality

Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, age or profession will be removed from the data and will be replaced with a 4-digit number composed by your date of birth (month and day). A list linking the 4-digit number with your name will be saved in a password protected Excel Spreadsheet that will be kept in a secure place, separate from your file. The data, with identifying information removed (only with the 4-digit number), will be securely stored in a locked office in the Department of Oncology. Information kept on a computer will be protected by a password. Once the study has been completed, the audio tapes will be destroyed in an appropriate manner. Once the study is complete, an archive of the data, without identifying information, will be kept for 10 years.

For the purpose of ensuring the proper monitoring of the research study it is possible that a member of the Hamilton Integrated Research Ethics Board and this institution and affiliated sites may consult your research data for quality assurance purposes. However, no records which identify you by name or initials will be allowed to leave the research office. By signing this consent form, you authorize such access.

Participation and Withdrawal

Your participation in this interview is completely voluntary and you are not obligated to complete it. You may skip any questions you prefer not to answer. All responses will be kept confidential and results will be presented in an anonymized format. **You are not being tested**, it is our material we are testing. **There are no right or wrong answers to our questions**. If you think something is easy or difficult, clear or confusing, if you understand or don't understand, we just want to know about it.

Information about the Study Results

I expect to have this study completed by November 2019. If you would like a brief summary of the results, please let me know how you would like it sent to you.

Questions about the Study

If you have questions or need more information about the study itself, please contact me at: florezid@mcmaster.ca or at: 613-562-5800 Ext. 8159

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HiREB). The HiREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, HiREB, at 905.521.2100 x 42013.

CONSENT

I have read the information presented in the information letter about a study being conducted by Ivan D. Florez, of McMaster University.

I have had the opportunity to ask questions about my involvement in this study and to receive additional details I requested.

I understand that if I agree to participate in this study, I may withdraw from the, study at any time. I will be given a signed copy of this form. I agree to participate in the study.

I would like to receive a summary of the study's results. *Yes* *No*

If yes, where would you like the results sent:

Email: _____

Mailing address: _____

_____

_____ _____ _____

Name of Participant (Printed) Signature Date

Consent form explained in person by:

_____ _____ _____

Name and Role (Printed) Signature Date

Appendix 3: Interviews' protocol

Research project Short title: ***Role of CPGs on drug funding decisions***

Date and Place:

Interviewee and Position:

Project description

"The aim of this study is to have an in-depth understanding of the role of CPG in decisions related to coverage and reimbursement of drug, in the health care system. We are interested in understanding how CPGs have been used by different types of decision makers/knowledge users. I will ask some open-ended questions and you will be free to respond giving as much detail as you desire. I will record the entire interview from the beginning. You are free to ask any questions and whenever you are ready, we can begin"

To before starting and with the aim of clarifying concepts and terms used during this interview, I will provide a definition of what clinical practice guidelines are." CPGs are systematically developed statements developed by a multidisciplinary group of people, informed by systematic reviews of evidence and an assessment of the benefits and harms of alternative care options with the aim of optimize patient care".

Interview Guide for Group 1 (*Synthesis* group)

- Do you create clinical practice guidelines? HTAs? Evidence briefs? Other types of outputs that include synthesis and appraisal of the clinical literature? Please specify….
- Do you produce (develop, adopt or adapt) your own CPGs or recommendations?
- Are you responsible for making available recommendations based on synthesized evidence that can be used by members of your group or other group to inform the drug funding decisions?
- How and what parts of the CPGs you produce/adopt/endorse are used by decision makers or committees to inform the process of drug funding analysis/review?

- Do these guidelines provide recommendations that are specifically tailored for drug funding decision making?

  Probe: when developing CPGs one of your aims is to provide recommendations that will be used for funding decisions?

- When you are preparing "evidence summaries" or "HTA reports" what parts or sections of CPGs are informing, or have been used to inform, the process of drug funding decisions by CADTH/the Ministry of Health?

  _ Recommendations

  _ Evidence tables or evidence summaries

  _ Reference or citations provided by the CPG

  _ Other?

- How CPGs or their recommendations are used in the drug funding decision process? How the recommendations inform the process?
- Why do you think CPGs are regularly used in this process?

  _ What would be the aim when using CPGs in this process?

  _ How CPGs are helping in the decision-making process?

- When thinking about the direction of the process by which the recommendations inform the decision-making, which one of the following would be the best summary of what commonly occurs:

  _ CPGs are the start of the process (there is an intention to choose the recommendations from CPG to make changes on the coverage, drugs list or packages)? (a "push" activity)

  _ CPGs are a source for decision-making (CPGs are consulted in response to the need for taking a decision on a specific drug or scenario) (a "pull" activity)

  _ A combination of the previous scenarios (sometimes CPGs are the trigger, and sometimes are a source of evidence/information)

  _ Any other?

- What conditions appear ***to favour*** the use of CPGs in the decision-making?

  _ *The (moderate or high) quality of the evidence?*

  _ *The strength of the recommendation?*

  _ *The time of Guideline publication?*

  _ *Consideration of policy, patients, guidelines or clinicians' values?*

  _ *The alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)*

  _ *The alignment of the CPG recommendation with the recommendation by PCODR?*

  _ *The source of the CPG?*

  _ *Characteristics of the organizations (e.g., CCO, CADTH, MoH, IETS?*

- What conditions appear ***to act against*** the use of CPGs in the decision-making?

  _ *The (low) quality of the evidence?*

  _ *The strength of the recommendation?*

  _ *The time of guideline publication?*

  _ _ *Consideration of policy, patients, guidelines or clinicians' values?*

  _ *The lack of alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)*

  _ *The lack of alignment of the CPG recommendation with the recommendation by PCODR?*

  _ *The source of the CPG?*

  _ *Characteristics of the organizations?*

- What would be the benefits and disadvantages of using CPGs for these decisions?
- Do you remember a specific drug case in which a positive or negative drug funding recommendation

may have been driven by a CPG recommendation?

- Do you remember a specific drug case in which a drug funding recommendation was not in the same direction of a CPG recommendation?
- Do you remember any article, book, report or other type of information may have information about the use of guidelines in these decisions in Colombia/Canada?

Interview Guide for Group 2 (*Prioritizers* group)

- Do you use, or have you used CPG produced by CCO-PEBC/MoH-IETS to inform the process of drug funding analysis/review?
- Could you please briefly describe how is, or have been, the process of prioritizing drugs that will be evaluated to be considered for funding decisions?
- When you are preparing evidence summaries or HTA what parts or sections of CPGs are or have been used to inform the process of drug funding decision by the Ministry of Health?

  _ *Recommendations*

  _ *Evidence tables or evidence summaries*

  _ *Reference or citations provided by the CPG*

  _ *Other?*

- How CPGs or their recommendations are used in the process of drug funding? How the recommendations inform the process?
- Why CPGs are regularly used in this process?

  _ *What would be the aim when using CPGs in this process?*

  _ *How CPGs are helping in the decision-making process?*

- When thinking about the direction of the process by which the recommendations inform the decision-making, which one of the following would be the best summary of what commonly occurs?

_ CPGs are the start of the process (there is an intention to choose the recommendations from CPG to make changes on the coverage, drugs list or packages)? (a "push" activity)

_ CPGs are a source for decision-making (CPGs are consulted in response to the need for taking a decision on a specific drug or scenario) (a "pull" activity)

_ A combination of the previous scenarios (sometimes CPGs are the trigger, and sometimes are a source of evidence/information)

_ Any other?

- What conditions appear ***<u>to favour</u>*** the use of CPGs in the decision-making?

  _ The (moderate or high) quality of the evidence?

  _ The strength of the recommendation?

  _ The time of Guideline publication?

  _ Consideration of policy, patients, guidelines or clinicians' values?

  _ The alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)

  _ The alignment of the CPG recommendation with the recommendation by PCODR?

  _ The source of the CPG?

  _ Characteristics of the organizations or institutions (e.g., CCO, CADTH, MoH, IETS?

- What conditions appear ***<u>to act against</u>*** the use of CPGs in the decision-making?

  _ The (low) quality of the evidence?

  _ The strength of the recommendation?

  _ The time of guideline publication?

  _ _ Consideration of policy, patients, guidelines or clinicians' values?

  _ The lack of alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)

  _ The lack of alignment of the CPG recommendation with the recommendation by PCODR?

  _ The source of the CPG?

_ *Characteristics of the organizations?*

- What would be the benefits and disadvantages of using CPGs for these decisions?
- Do you remember a specific drug case in which a positive or negative drug funding recommendation may have been driven by a CPG recommendation?
- Do you remember a specific drug case in which a drug funding recommendation was not in the same direction of a CPG recommendation?
- Do you remember any article, book, report or other type of information may have information about the use of guidelines in these decisions in Colombia/Canada?

Interview Guide for Group 3 (*Decision* group)

- Do you use, or have you used CPG produced by CCO-PEBC/MoH-IETS to inform the process of drug funding analysis/review?
- How CPGs or their recommendations are used in the process of drug funding? How the recommendations inform the process?
- Why do you think CPGs are regularly used in this process?

  _ *What would be the aim when using CPGs in this process?*

  _ *How CPGs are helping in the decision-making process?*

- When thinking about the direction of the process by which the recommendations inform the decision making, which one of the following would be the best summary of what commonly occurs:

  _ *CPGs are the start of the process (there is an intention to choose the recommendations from CPG to make changes on the coverage, drugs list or packages)? (a "push" activity)*

  _ *CPGs are a source for decision-making (CPGs are consulted in response to the need for taking a decision on a specific drug or scenario) (a "pull" activity)*

_ *A combination of the previous scenarios (sometimes CPGs are the trigger, and sometimes are a source of evidence/information)*

_ *Any other?*

- What conditions appear ***<u>to favour</u>*** the use of CPGs in the decision-making?

  _ *The (moderate or high) quality of the evidence?*

  _ *The strength of the recommendation?*

  _ *The time of Guideline publication?*

  _ *Consideration of policy, patients, guidelines or clinicians' values?*

  _ *The alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)*

  _ *The alignment of the CPG recommendation with the recommendation by PCODR?*

  _ *The source of the CPG?*

  _ *Characteristics of the organizations (e.g., CCO, CADTH, MoH, IETS?*

- What conditions appear ***<u>to act against</u>*** the use of CPGs in the decision-making?

  _ *The (low) quality of the evidence?*

  _ *The strength of the recommendation?*

  _ *The time of guideline publication?*

  _ _ *Consideration of policy, patients, guidelines or clinicians' values?*

  _ *The lack of alignment of the CPG recommendation with the interests of stakeholders? (e.g., patient's advocacy groups, clinicians)*

  _ *The lack of alignment of the CPG recommendation with the recommendation by PCODR?*

  _ *The source of the CPG?*

  _ *Characteristics of the organizations?*

- What would be the benefits and disadvantages of using CPGs for these decisions?
- Do you remember a specific drug case in which a positive or negative drug funding recommendation

may have been driven by a CPG recommendation?

- Do you remember a specific drug case in which a drug funding recommendation was not in the same direction of a CPG recommendation?

Appendix 4: Colombian evidence reports used for the update of the benefit package in 2013

#	Interventions evaluated	Full title (Spanish)	Used information from the CPGs (Synthesis)	Mentioned the use of CPG for developing the Review question	Mentioned the use of CPG for developing the Review question	Mentioned at least one CPGs in background	Mentioned at least one CPG in the description of therapy lines or question development	Mentioned at least one CPG in the discussion	At least one CPGs is cited (references)	Link
1	Ablación por radiofrecuencia	Efectividad y seguridad de la ablación por radiofrecuencia en taquicardia supraventricular		X	X			X	X	http://www.iets.org.co/Archivos/Ablaci%C3%B3n_por_radiofrecia_26112013.pdf
2	Brimonidina con timolol	Efectividad y seguridad de la combinación de brimonidina con timolol para el tratamiento de glaucoma de ángulo abierto y cerrado y de la hipertensión ocular		X	X			X	X	http://www.iets.org.co/Archivos/Glaucoma%20(brimonidina%20m%C3%A1s%20timolol).pdf
3	Carboximetil celulosa	Efectividad y seguridad de carboximetil celulosa tópica para el tratamiento sintomático del ojo seco.		X	X					http://www.iets.org.co/Archivos/S%C3%ADndrome%20de%20ojo%20seco%20(l%C3%A1grimas%20artificiales).pdf
4	Cefaclor, cefprozil y cefuroxima	Evaluación de efectividad y seguridad de cefaclor, cefprozil y cefuroxima como primera línea para neumonía adquirida en la comunidad en menores de 5 años		X	X				X	http://www.iets.org.co/Archivos/Neumon%C3%ADa%20Adquirida%20en%20Comunidad%20(cefprozilo%20y%20cefaclor).pdf
5	Cefotaxima	Efectividad y seguridad de cefotaxima como primera línea para el tratamiento intrahospitalario asociada a la complicada por pneumoniae resistente en niños		X	X				X	http://www.iets.org.co/Archivos/EyS%20Cefotaxima%20y%20ceftriaxona_26112013.pdf
6	Deferasirox	Evaluación de efectividad y seguridad de deferasirox en Hemosiderosis Transfusional		X	X			X	X	http://www.iets.org.co/Archivos/EyS%20Hemosiderosis%20transfusional%20(deferasirox).pdf
7	Dexrazoxano	Efectividad y seguridad de dexrazoxano para prevenir el daño cardíaco en pacientes menores de 18 años con Linfoma Hodgkin o Leucemia linfoide aguda, en quimioterapia con antraciclinas.	X	NA	NA	NA	NA	NA	NA	http://www.iets.org.co/Archivos/FR%20Dexrazoxano.pdf
8	Donepezilo, galantamina y memantina	Efectividad y seguridad de donepezilo, galantamina y memantina		X	X			X		http://www.iets.org.co/Archivos/EyS Donepezilo_09122013.pdf

		para el tratamiento de la Enfermedad de Alzheimer								
9	Dorzolamida	Efectividad y seguridad de dorzolamida para el tratamiento de glaucoma de ángulo abierto y cerrado y de la hipertensión ocular		**X**	**X**			**X**	**X**	http://www.iets.org.co/Archivos/EyS%20Glaucoma%20(Dorzolamida).pdf
10	Epirrubicina	Efectividad y seguridad de epirubicina para el tratamiento de cáncer gástrico resecable		**X**	**X**		**X**		**X**	http://www.iets.org.co/Archivos/EyS%20Epirrubicina_26112013.pdf
11	Estramustina	Efectividad y seguridad de la estramustina para el tratamiento de pacientes con cáncer de próstata avanzado hormono-refractario.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Estramustina.pdf
12	Finasterida	Evaluación de efectividad y seguridad de finasterida, para el tratamiento en hiperplasia benigna de próstata		**X**	**X**	**X**				http://www.iets.org.co/Archivos/EyS%20Hiperplasia%20benigna%20de%20pr%C3%B3stata%20(finasteride).pdf
13	Fondaparinux, enoxaparina y heparina no fraccionada	Efectividad y seguridad de fondaparinux comparado con enoxaparina y heparina no fraccionada, en pacientes mayores de 18 años con Síndrome Coronario Agudo (SCA).	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Fondaparinux.pdf
14	Fulvestrant, anastrazol y exemestane	Efectividad y seguridad de fulvestrant comparado con anastrazol y exemestane, en mujeres posmenopáusicas con cáncer de mama metastásico o recurrente, receptor hormonal positivo, con falla a la terapia hormonal con inhibidores de aromatasa.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Fulvestrant.pdf
15	Gabapentina y pregabalina	Efectividad y seguridad de gabapentina y pregabalina como monoterapia de primera línea en adultos con dolor neuropático		**X**	**X**					http://www.iets.org.co/Archivos/EyS%20Dolor%20neurop%C3%A1tico%20(gabapentina%20y%20pregabalina).pdf
16	Hemicolectomía derecha por laparoscopial.	Efectividad y seguridad del tratamiento con hemicolectomía derecha por laparoscopia para cáncer colorectal.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Hemicolectomia%20laparosc%C3%B3pica.pdf
17	Inhibidores de aromatasa (anastrazol,	Efectividad y seguridad de la terapia hormonal con inhibidores de aromatasa (anastrazol, letrozol,	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Fulvestrant.pdf

	letrozol, exemestane)	exemestane) en mujeres postmenopáusicas con cáncer de mama temprano y localmente avanzado, receptor hormonal positivo.								
18	Inmunoterapia	Efectividad y seguridad de la inmunoterapia en el tratamiento del asma complicada en niños.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Inmunoterapia%20subcut%C3%A1nea.pdf
19	Interferón ß1a recombinante, interferón ß1b, acetato de glatiramer, natalizumab y fingolimod	Efectividad y seguridad del Interferón ß1a recombinante, interferón ß1b, acetato de glatiramer, natalizumab y fingolimod para la prevención de la progresión de la discapacidad en adultos con esclerosis múltiple de tipo recaída-remisión o secundaria progresiva		**X**	**X**					http://www.iets.org.co/Archivos/Efectividad%20y%20Seguridad%20interferones.pdf
20	Levofloxacina y moxifloxacina	Efectividad y seguridad de levofloxacina y moxifloxacina, como monoterapia ambulatoria para neumonía asociada a la comunidad en adultos		**X**	**X**	**X**			**X**	http://www.iets.org.co/Archivos/EyS%20Neumon%C3%ADa%20adquirida%20en%20comunidad%20(levofloxacina%20y%20moxifloxacina).pdf
21	Metilprednisolona	Efectividad y seguridad de metilprednisolona en el tratamiento del asma en niños.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/DocTecnicos/FrmPublicacion.aspx?idarticulo=1184
22	Metoprolol	Efectividad y seguridad de metoprolol para pacientes con síndrome coronario agudo.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Metoprolol.pdf
23	Montelukast	Efectividad y seguridad de montelukast para el tratamiento del asma en niños.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Montelukast.pdf
24	Nebivolol	Efectividad y seguridad de nebivolol como tratamiento ambulatorio de primera línea para isquemia miocárdica, no complicada, en adultos		**X**	**X**			**X**	**X**	http://www.iets.org.co/Archivos/EyS%20Isquemia%20mioc%C3%A1rdica%20no%20complicada%20(nebivolol).pdf
25	Oxcarbazepina, vigabatrina, levetiracetam	Efectividad y oxcarbazepina, vigabatrina, levetiracetam como terapia adjunta para el tratamiento de segunda línea en pacientes con epilepsia refractaria		**X**	**X**			**X**	**X**	http://www.iets.org.co/Archivos/EyS%20Epilepsia%20refractaria.pdf
26	Palivizumab	Efectividad de palivizumab para la reducción de riesgo de infección	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Palivizumab.pdf

		respiratoria por Virus Sincitial Respiratorio (VSR) en el recién nacido prematuro.								
27	Paroxetina, escitalopram y fluvoxamina	Efectividad y seguridad de paroxetina, escitalopram y fluvoxamina como tratamiento farmacológico de primera línea para depresión moderada y severa en población mayor de 18 años.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Paroxetina,%20escitalopram%20y%20fluvoxamina.pdf
28	Pramipexol	Efectividad y seguridad de pramipexol para el tratamiento de la enfermedad de Parkinson de inicio temprano		**X**	**X**	**X**		**X**	**X**	http://www.iets.org.co/Archivos/EyS%20Enfermedad%20de%20Parkinson%20temprana%20(pramipexol).pdf
29	Prostatectomía por laparoscopia	Efectividad y seguridad de la prostatectomía por laparoscopia para el tratamiento del cáncer de próstata localizado.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Prostatectomia%20por%20laparoscopia.pdf
30	Quimioterapia con el esquema mitoxantrone más corticosteroides	Efectividad y seguridad de la quimioterapia con el esquema mitoxantrone más corticosteroides para el manejo de cáncer de próstata hormono-refractario.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Mitoxantrone.pdf
31	Radioterapia conformacional	Efectividad y seguridad de la radioterapia conformacional en cáncer gástrico		**X**	**X**			**X**	**X**	http://www.iets.org.co/Archivos/EyS%20C%C3%A1ncer%20g%C3%A1strico%20(radioterapia%20conformacional%203D).pdf
32	Riluzol	Evaluación de efectividad y seguridad de riluzol como tratamiento para prolongar el tiempo libre de traqueostomia en pacientes con esclerosis lateral		**X**	**X**				**X**	http://www.iets.org.co/Archivos/EyS%20Esclerosis%20lateral%20amiotr%C3%B3fica%20(riluzol).pdf
33	Risperidona	Efectividad y seguridad de risperidona en terapia combinada con estabilizadores del ánimo en personas con trastorno afectivo bipolar.		**X**	**X**					http://www.iets.org.co/Archivos/EyS%20trastorno%20afectivo%20bipolar.pdf
34	Salmeterol y formoterol	Efectividad y seguridad de salmeterol y formoterol en el tratamiento de asma en niños.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/Salmeterol%20y%20formoterol.pdf
35	Somatostatina, octreotida y terlipresina	Efectividad y seguridad de somatostatina comparada con octreotida y terlipresina para el		**X**	**X**			**X**		http://www.iets.org.co/Archivos/EyS%20V%C3%A1rices%20e

		control de la hemorragia de vías digestivas altas en adultos con várices esofágicas								sof%C3%A1gicas%20(somatostatina).pdf
36	Somatropina	Efectividad y seguridad de somatropina para el tratamiento del retardo de crecimiento en niños menores de 18 años con insuficiencia renal crónica		**X**	**X**				**X**	http://www.iets.org.co/DocTecnicos/FrmPublicacion.aspx?idarticulo=1200
37	Stent duodenal	Evaluación de efectividad y seguridad del stent duodenal para el manejo de la obstrucción tumoral del vaciamiento gástrico en cáncer gástrico avanzado		**X**	**X**			**X**	**X**	http://www.iets.org.co/Archivos/EyS%20C%C3%A1ncer%20g%C3%A1strico%20avanzado%20(stent%20duodenal).pdf
38	Stent medicado	Efectividad y seguridad del stent medicado para pacientes con síndrome coronario agudo	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/Fr%20Stent%20medicado.pdf
39	Tacrolimus	Efectividad y seguridad de tacrolimus como inmunosupresión primaria en receptores de trasplante renal.		**X**	**X**					http://www.iets.org.co/Archivos/EyS%20Trasplante%20renal%20(tacrolimus).pdf
40	Terapia biológica	Terapia biológica para el tratamiento de pacientes con artritis reumatoide refractaria.		**X**	**X**		**X**	**X**		http://www.iets.org.co/Archivos/Biol%C3%B3gicos%20en%20AR%20refractaria.pdf
41	Timolol en combinaciones y dorzolamida	Efectividad y seguridad de timolol en combinaciones y dorzolamida en combinaciones para el tratamiento de glaucoma de ángulo abierto y cerrado y de la hipertensión ocular		**X**	**X**				**X**	http://www.iets.org.co/Archivos/EyS%20Glaucoma%20(timolol%20combinaciones%20y%20dorzolamida%20combinaciones).pdf
42	Travoprost	Efectividad y seguridad de travoprost para el tratamiento de glaucoma de ángulo abierto y cerrado y de la hipertensión ocular		**X**	**X**				**X**	http://www.iets.org.co/Archivos/EyS%20Glaucoma%20(travoprost).pdf
43	Zinc	Efectividad y seguridad de la suplementación con zinc para el tratamiento de la enfermedad diarreica aguda en niños y niñas menores 5 años.	**X**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	http://www.iets.org.co/Archivos/FR%20Documento%20de%20Evaluacion%20-%20Zinc.pdf

Cells in grey shows the technologies and drugs that did not have a full evidence review, and instead the CPG was used to inform the decision-making process. These were short reports developed with CPG information, and thus, the rest of the categories did not apply. NA: Not applicable.

Appendix 5. Clinical and economic guidance reports developed by CADTH during 2018 and 2019 and the role of CPGs

pCODR ID	Intervention and indication	referencing guidelines (Y/N)	Initial CGR	Final CGR	Final recommendation	Clinician Feedback	Sponsor feedback	Manufacturer feedback	link:
10182	Trastuzumab emtansine EBC	N							https://cadth.ca/cemiplimab-libtayo-cutaneous-squamous-cell-carcinoma-details
10187	Ccmiplimab CSCC	N							https://cadth.ca/cemiplimab-libtayo-cutaneous-squamous-cell-carcinoma-details
10176	Pembrolizumab squamous NSCLC	N							https://cadth.ca/keytruda-squamous-nsclc-details
10174	Olaparib OC	Y		X		X			https://cadth.ca/lynparza-newly-diagnosed-ovarian-cancer-details
10172	Neratinib EBC	N							https://cadth.ca/nerlynx-hormone-receptor-positive-breast-cancer-details
10189	Daratumumab MM		X						https://cadth.ca/daratumumab-darzalex-multiple-myeloma
10183	Lorlatinib NSCLC	N							https://cadth.ca/lorlatinib-lorbrena-non-small-cell-lung-cancer-details
10156	Atezolizumab SCLC	Y			X		X		https://cadth.ca/tecentriq-small-cell-lung-cancer-details
10159	Larotrectinib NTRK positive solid tumours	N							https://cadth.ca/larotrectinib-neurotrophic-tyrosine-receptor-kinase-ntrk-locally-advanced-or-metastatic-solid
10144	Enasidenib AML	Y		X			X		https://cadth.ca/idhifa-acute-myeloid-leukemia-details
10177	Pembrolizumab MUC	N							https://cadth.ca/keytruda-metastatic-urothelial-carcinoma-first-line-details
10165	Pomalidomide MM	N							https://cadth.ca/pomalyst-combination-dexamethasone-and-bortezomib-multiple-myeloma-second-line-or-beyond-details
10173	Trifluridine-tipiracil mcrpc resub	N							https://cadth.ca/trifluridine-and-tipiracil-lonsurf-metastatic-colorectal-cancer-resubmission-details
RFA0002	Bosutinib CML	Y	X					X	https://cadth.ca/rfa-bosulif-chronic-myeloid-leukemia-details

10168	**Pembrolizumab MAT**	**Y**		**X**					https://cadth.ca/keytruda-melanoma-adjuvant-treatment-details
10172	**Lutetium dotatate gepnets**	**N**							https://cadth.ca/lutathera-gastroenteropancreatic-neuroendocrine-tumors-details
10167	**Brigatinib ALK+ NSCLC**	**N**							https://cadth.ca/brigatinib-alunbrig-non-small-cell-lung-cancer-nsclc-details
10148	**Daratumumab MM**	**N**							https://cadth.ca/darzalex-combo-bortezomib-melphalan-and-prednisone-multiple-myeloma-newly-diagnosed-details
10175	**Lenvatinib HCC**	**Y**		**X**	**X**				https://cadth.ca/lenvima-hepatocellular-carcinoma-details
10164	**Ixazomib MM resub**	**N**							https://cadth.ca/ninlaro-multiple-myeloma-2nd-beyond-details
10161	**Abamaciclib breast cancer**	**Y**		**X**					https://cadth.ca/abemaciclib-advanced-or-metastatic-breast-cancer-details
10140	**Lenvatinib RCC**	**Y**		**X**					https://cadth.ca/lenvima-renal-cell-carcinoma-details
10141	**Lenalidomise MM**	**N**							https://cadth.ca/revlimid-combo-bortezomib-dexamethasone-newly-diagnosed-multiple-myeloma-details
10162	**Venetoclax+rituximab CLL**	**N**							https://cadth.ca/venclexta-combo-rituximab-chronic-lymphocytic-leukemia-details
10153	**Pembrolizumab+chemo nonsquamous NSCLC**	**Y**		**X**					https://cadth.ca/keytruda-non-squamous-nsclc-details
10129	**Dacomitinib EGFR+ NSCLC**	**N**							https://cadth.ca/vizimpro-non-small-cell-lung-cancer-details
10151	**Crizotinib ROS1 NSCLC**	**Y**		**X**					https://cadth.ca/xalkori-ros1-positive-advanced-non-small-cell-lung-cancer-details
10152	**Dabrafenib-trametinib MAT**	**N**							https://cadth.ca/tafinlar-mekinist-combo-melanoma-adjuvant-therapy-details
10131	**Durvalumab adjuvant NSCLC**	**N**							https://cadth.ca/imfinzi-non-small-cell-lung-cancer-details
10150	**Palbociclib+fulvestrant breast cancer**	**Y**		**X**					https://cadth.ca/ibrance-faslodex-advanced-or-metastatic-breast-cancer-details
10138	**Pralatrexate PTCL**	**N**							https://cadth.ca/folotyn-peripheral-t-cell-lymphoma

10146	**Blinatumomab Ph+ ALL**	**N**							https://cadth.ca/blincyto-philadelphia-chromosome-positive-b-cell-precursor-acute-lymphoblastic-leukemia-details
10149	**Enzalutamide nmcrpc**	**Y**		**X**					https://cadth.ca/xtandi-non-metastatic-castration-resistant-prostate-cancer-details
10145	**Brentuximab HL resub**	**N**							https://cadth.ca/adcetris-hodgkin-lymphoma-resubmission-details
10147	**Nivolumab MAT**	**N**							https://cadth.ca/opdivo-melanoma-adjuvant-therapy-details
10154	**Dinutuximab neuroblastoma**	**N**							https://cadth.ca/unituxin-neuroblastoma-details
10163	**Cabozantinib RCC**	**Y**		**X**					https://cadth.ca/cabometyx-renal-cell-carcinoma-resubmission-details
10137	**Osimertinib NSCLC**	**N**							https://cadth.ca/tagrisso-non-small-cell-lung-cancer-first-line-details
10134	**Nivolumab HCC**	**N**							https://cadth.ca/opdivo-hepatocellular-carcinoma-details
10127	**Pertuzumab+trastuzumab breast cancer**	**Y**			**X**				https://cadth.ca/perjeta-herceptin-combo-pack-early-breast-cancer-details
10133	**Apalutamide nmcrpc**	**N**							https://cadth.ca/erleada-castrate-resistant-prostate-cancer-details
10132	**Nivolumab+ipilimumab RCC**	**Y**		**X**					https://cadth.ca/opdivo-combo-yervoy-renal-cell-carcinoma-details
10126	**Obinuzumab FL**	**Y**		**X**					https://cadth.ca/gazyva-follicular-lymphoma-previously-untreated-details
10125	**Alectinib ALK+ NSCLC 1st line**	**Y**		**X**					https://cadth.ca/alecensaro-non-small-cell-lung-cancer-first-line-details
10121	**Inotuzumab ozogamicin ALL**	**N**							https://cadth.ca/besponsa-acute-lymphoblastic-leukemia-details
10122	**Trifluridine-tipiracil mcrpc**	**N**							https://cadth.ca/lonsurf-metastatic-colorectal-cancer-details
10114	**Alectinib metastatic NSCLC**	**N**							https://cadth.ca/alecensaro-locally-advanced-or-metastatic-non-small-cell-lung-cancer-second-line-details
10107	**Irenotecan liposome mpc**	**Y**		**X**					https://cadth.ca/onivyde-metastatic-pancreatic-cancer-details
10115	**Atezolizumab previously treated NSCLC**	**N**							https://cadth.ca/tecentriq-non-small-cell-lung-cancer-details

10120	**Nivolumab chl**	**N**							https://cadth.ca/opdivo-classical-hodgkin-lymphoma-after-failure-asct-details
10119	**Regorafenib HC**	**N**							https://cadth.ca/stivarga-unresectable-hepatocellular-carcinoma-hcc-details
10111	**Olaratumumab soft tissue sarcoma**	**Y**		**X**					https://cadth.ca/lartruvo-advanced-soft-tissue-sarcoma-details
10112	**Ribociclib breast cancer**	**N**							https://cadth.ca/kisqali-metastatic-breast-cancer-details
10114	**Alectinib 2nd line NSCLC**	**N**							https://cadth.ca/alecensaro-locally-advanced-or-metastatic-non-small-cell-lung-cancer-second-line-details
10118	**Panitumumab left-sided mcrc**	**Y**		**X**					https://cadth.ca/vectibix-left-sided-metastatic-colorectal-cancer-details
10105	**Venetoclax CLL**	**N**							https://cadth.ca/venclexta-chronic-lymphocytic-leukemia-details
10124	**Avelumab mmcc**	**N**							https://cadth.ca/bavencio-metastatic-merkel-cell-carcinoma-details
10117	**Pembrolizumab MUC**	**N**							https://cadth.ca/keytruda-metastatic-urothelial-carcinoma-details
10116	**Brentuximab HL**	**N**							https://cadth.ca/adcetris-hodgkins-lymphoma-post-asct-resubmission-details
10110	**Fulvestrant MBC**	**Y**		**X**					https://cadth.ca/faslodex-locally-advanced-or-metastatic-breast-cancer-details

CHAPTER 5. CONCLUSIONS

Chapter 5. Conclusions

The three original research studies presented in chapters 2, 3 and 4 of this thesis contribute to an increased understanding of the roles of CPGs in the activities and decisions outside the clinical encounter. This work adds to research investigation with its unique lens of examining the roles and the impacts of CPGs outside this traditional context. Additionally, I applied three different research designs to address the three primary research questions. I created an explanatory framework, designed a survey informed by the framework, and I focused on one role (drug funding decisions) to study in depth how and under what conditions CPGs were used. In this final chapter I summarize the principal findings from the thesis, as well as strengths and limitations, implications for research, policy and practice, and provide final remarks.

Principal findings

This thesis is grounded on different methodological approaches to respond three overarching objectives related to the describing and understanding the role of CPGs outside the clinical encounter. In chapter 1, I provided a brief overview of the CPGs and how they evolved from solely consensus, to solely evidence-based recommendations, to where they are now, continuing to optimize the strengths, of various methods, and perspectives to ensure quality, rigor and implementability. The focus of this overview was on their traditional role within the clinical encounter. This chapter then introduced the focus of my program of research to address how CPGs are being used for other purposes and the roles of actors in this context extending beyond clinicians and patients.

In chapter 2, I applied a critical interpretive synthesis (CIS) methodology to develop a theoretical framework that describes what are the activities in which CPGs play roles outside the clinical encounter and explains how, and under what conditions these roles are played. I identified that 15 activities outside the clinical encounter and categorized them according to their importance using the terms main roles, secondary roles, and an unanticipated role. The two main roles I identified are quality of care and

economic decisions, the two secondary roles are medical education, maintenance of certification and licensing, and research prioritization, and one unanticipated role, the judicial decisions.

In chapter 3, I conducted an international online survey focused on organizations or groups that regularly produce CPGs. Using the activities emerging from the CIS, participants were asked whether the CPGs they produced were used for any of these additional roles. Developers commonly reported that CPGs are often used to inform activities aimed to improve quality of care; to support coverage decisions; and to inform research prioritization, medical education and licensing activities. The less frequently chosen activity was to inform judicial decisions. All respondents reported that their CPGs are used for at least one role and most of them reported that CPGs are commonly used in many roles outside the clinical encounter. Moreover, respondents reported that these roles were formally recognized in the aims or scope of their CPG development programs and that this resulted in engaging stakeholders from these various fields in the CPG development process.

In chapter 4, I performed a multiple case study to investigate in depth one of the main alternative roles of CPGs, informing *economic decisions*, specifically for drug funding decisions. With the aim to understand whether CPGs are used, and how and under what conditions they are used in drug funding decisions, I studied two cases. The first case was Colombia that is comprised of a single national strategy of evidence production, recommendations, decisions, and ultimate drug funding decisions. The second case was Canada/Ontario that uses two jurisdictional levels - national and provincial roles - in drug funding decisions. I described how the role of CPGs in drug funding decisions was critical in the Colombian case, while it was limited in the Canada/Ontario case. I also studied how CPGs have been used, and I found that their use was instrumental (CPGs recommendations were used to directly inform the process and decide whether or not a drug should be funded), conceptual (CPGs are cited and were used to inform some steps, such as the design of the review question, or to discuss the results of the decision), and symbolic (CPGs that align with the funding decision end up being used as a back-up to

help decision-makers to support their already taken decisions) in Colombia and only conceptual and symbolic in Canada/Ontario

Lastly, to understand under what conditions CPGs have been used, I applied the "3Is" framework in both cases. This political science framework allowed the analysis of the factors that may have influenced in favour or against of the instrumental, conceptual or symbolic uses of CPGs. The framework categorizes the following domains: ideas (values and beliefs), interests (political interests and interests' groups) and institutions (Government structure and policy legacies). The instrumental use of CPGs in Colombia (CPGS were used to directly inform what drugs should be funded) is explained by policy legacies, political positions and specific beliefs around evidence and CPGs. The conceptual use of CPGs in /OntarioCanada is limited to inform the writing of the drug evidence reports and support the development of the review PICO (population, intervention, comparison and outcome) questions. In both cases, the symbolic use, was present, when CPGs were used after decisions were taken as a support for them, when available CPGs aligned with those decisions.

This work presents results that are unique in the literature. Each of the three studies is the first one in responding each question. Although the literature is plenty of articles that describe the roles of CPGs, the CIS (chapter 2) is the first comprehensive review on the topic and the framework is the only available resource thar has summarized all these roles. Also, the chapter 3 presents the first survey that has investigated how do developers perceive the roles of CPGs in their contexts. Finally, the chapter 4 presents the first in depth study on how CPGs are used to inform drug-funding decisions and also, is the first study that has evaluated this question.

Strengths and limitations

Together, these three studies have several strengths to highlight. First, this is the first time that I am aware that the roles of CPGs outside the clinical encounter are studied. Although, CPGs are ubiquitous,

and are commonly used in many settings in and out the clinical encounter, this program of research provides a systematic, comprehensive, and deep understanding of how they are used and under what conditions. Until now, the literature on the topic has been limited to describe that CPGs are or may be useful for many roles, but this information largely comes from either narrative reviews, editorial letters or viewpoints that summarizes the potential roles, or from specific-roles studies or reviews (1-6). Also, some reviews have focused on one role, such as those focused on summarizing the tools and approaches used to create quality indicators from CPGs (7-9). However, this CIS is the first evidence synthesis that covered all the roles and summarized them and identified how they are used and what are the gaps that need further research in the methods and approaches to link recommendations to specific roles.

Second, my survey allowed me to put in context the findings from the CIS. Thus, in addition to provide the first ever evidence synthesis on the roles of CPGs, I am also presenting the first international survey on the topic. Together, CIS and survey, provide an understanding of what literature has described in the last three decades, and an in-time analysis of how frequent these roles are occurring globally according to the report from international developers.

Third, the case study is the first in-depth analysis of how CPGs may play different roles in the drug funding process. Our study provided an understanding of the reasons that explained the conditions under which CPGs play a major instrumental role in the Colombia context and a conceptual use in the Ontario-Canada context. Moreover, this study allowed me to do rich comparisons within and between jurisdictions.

As whole, this thesis has a final strength. There is a strong link among the three studies. As stated, the CIS summarized the evidence, the survey described the status of the roles across the globe, and the case study allowed me to understand one of the main roles of CPGs outside the clinical encounter, the drug funding decisions. This combination of methods to respond to different but strongly related questions strengthen my findings.

This program of research has some limitations. First, CIS only included literature in English, Spanish, French and German. Although these languages may include the majority of papers covering the topic of CPGs, important and relevant papers in other languages may have been missed. Second, in the survey I invited almost 200 organizations to participate and could only obtain 39.4% or response rate. However, the obtained responses were from organizations representing 32 countries, from both, high and low-middle income settings, lending confidence that I obtained information that might be extrapolated to settings that were not represented in the survey. Nonetheless, a higher response rate would have been preferred.

Additionally, in the case study I focused on a single jurisdictional national level process (Colombia) and a dual jurisdictional context, national-provincial in the Canada/Ontario case. Moreover, both cases were focused on different time periods (Colombia between 2011-2016, Canada/Ontario 2011-2019) and on relatively different processes (in Colombia, it was an overall drug funding process, while in Canada it was on the cancer drugs drug funding process). Thus, the cases may be too discordant considered different to be contrasted. These differences were necessary to capture the richest events that would inform the analyses in each country, and I was interested in understanding two different jurisdictions and in obtaining meaningful learnings from their differences and similarities.

Lastly, a final limitation of the case study is the number of participants. Although I invited a relative long list of key potential participants, I was not successful in many cases. Some participants declined the invitations, others did not accept, and others accepted but it was not possible to arrange a meeting for interview due their busy schedule. Nonetheless, I obtained the participation of key individuals from both cases and saturation of concepts and ideas were met with the methods used.

Implications for research, practice and policy

The results of my CIS will be very useful for future research. My framework categorizes the roles as main, secondary and unintended, and the framework that summarizes what methods and approaches are available will be key for researchers interested in improving the CPGs methodology. For instance, researchers might want to identify the areas that require total or partial methodological development (such as the role in educational tool, maintenance of certification, in economic decisions, or in research prioritization) to better meet the needs of the intended purpose. A single CPG develop methodology or presentation style may not be appropriate for all users in all contexts. Also, further testing of my framework in future projects is another research need.

Other stakeholders will be interested in the results from the CIS. With the framework, I am raising awareness into many roles that may have been neglected or limited in some contexts. Different stakeholders may start using CPGs to inform activities for which CPGs were not initially used. Research funding organizations for instance, can identify the best methods to link recommendations to inform research prioritization processes. More formal links between developers and research funding bodies may enable the latter insights into care options resulting in weak recommendations due to poor quality and/or scarce research evidence. Accordingly, research funding could be directed to these topics to build the primary evidence base. This might make the research prioritization process more efficient and more targeted to the most clinically relevant questions.

The results from my survey will also be useful for guidelines and implementation researchers. They could study the roles that are more or less frequently reported in their context, design studies to understand how some of these roles are occurring, or explore how these roles influence development methods, or uptake of recommendations for other purposes. Also, more studies focused in specific contexts were certain roles were frequently reported (e.g., economic decisions), may be designed further to understand how CPGs play this role. Moreover, as with the CIS, the survey helps in increasing awareness on some roles. Different stakeholders can identify how frequent these roles are reported by

developers. This will definitely help in building a critical mass of decision-makers who use evidence more explicitly in their contexts

Lastly, the results from the case study have highlighted how two jurisdictions can have entirely different uses for CPGs regarding drug funding decisions. Researchers interested in how CPGs might be improved can use our results to design further studies to try to better understand the perceptions of decision-makers in other contexts about the CPGs and how they are used. For instance, case studies in other countries can identify whether or not CPGs inform drug funding decisions, how they are used and whether the use is instrumental, conceptual or symbolic. If the instrumental use is replicated in other contexts, researchers can consider those results to improve the guideline development methods to enhance this use by creating recommendations that may be targeted to clinicians but also to decision-makers.

Policymakers can also benefit from these results. Our framework may highlight additional roles in which CPGs may be used, and they have not been considered. Policymakers can use the framework to take full advantage of CPGs in their contexts. Our survey results can also inform policymakers that are interested in developing or enhancing their CPGs development programs to better define the scope and target users of their CPGs. Also, policymakers that either use or do not use CPGs in drug funding decisions, may learn from the experiences summarized in the case study, and implement changes in their processes according to their necessities and the availability of trustworthy and context relevant CPGs. For instance, considering both CPGs plus CEA might be an approach that may work in some contexts where this is possible. Also, addressing some of the challenges that were pointed out by participants, such as improving guidelines quality, and enhancing the handling of conflicts of interests, could make CPGs more useful in some contexts to inform their drug funding decisions.

Finally, CPGs developers will be able to take advantages of these results. Developers might want to improve the definition of their target users in their final CPG document using our roles' framework. Additionally, with our framework about how CPGs play these roles, developers can consider the development of some improvements to their CPG methods. For example, if developers are interested in

expanding their users, they could develop some pre-publication changes (such as, better describing the research recommendations and how to address the identified research gap) to facilitate the use of CPGs as a research prioritization tool. Also, developers could use our case study results to improve their methodology by addressing the some of the limitations highlighted in both cases (e.g., handling of conflicts of interests, or reducing the development time).

Final remarks

This thesis dissertation provides the first in-depth study of the roles of CPGs outside the clinical encounter. With a CIS, I created a framework that summarizes possible roles and defined what are the areas that need further methodological development for those roles to be optimized. Based on the framework, I designed a survey that allowed me to identify and understand the current status of how frequently CPGs play roles in different countries. Lastly, I chose one main role (drug funding decisions) and studied in depth, through a multiple case study, whether it was present in two different countries, how CPGs have been used and under what conditions.

In conclusion, CPGs are certainly not only for informing decisions at the clinical encounter level. The roles of CPGs outside the clinical encounter are many, and they proved to be extremely common. The extent to which every CPG panel and every CPG development organization is aware about this wide scope of purpose for their recommendations is unclear. In some cases, developers may have this as part of their formal guideline remit and protocol. In other cases, how CPGs are used and by whom may not be clear or explicit. Clarity of purpose, intent, and target users can enable the conservations to happen between developers and users to ensure the final product, the CPG, fits to purpose

The scope of the CPGs, the potential users, and the degree to which CPGs can inform other activities have been a neglected issue in the CPGs field. This work can be the start of new research area by which guidelines researchers can develop new research projects focused on improving not only the

methods for CPGs development but also their usefulness for other roles. I believe filling these gaps will lead to an increase in the usefulness and efficiency of CPGs, will reduce duplication efforts and will contribute to improving population, patients and health system outcomes.

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