

ORIGINAL ARTICLE

Systematic reviews of clinical practice guidelines: a methodological guide

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Abstract

Objectives: Systematic reviews (SRs) of clinical practice guidelines (CPGs) are unique knowledge syntheses that require tailored approaches to, and greater subjectivity in, design and execution compared with other SRs in clinical epidemiology. We provide review authors structured direction on how to design and conduct methodologically rigorous SRs of CPGs.

Study Design and Setting: A guidance paper outlining suggested methodology for conducting all stages of an SR of CPGs. We present concrete examples of approaches used by published reviews, including a case exemplar demonstrating how this methodology was applied to our own SR of CPGs.

Results: Review context and the unique characteristics of CPGs as research syntheses or clinical guidance statements must be considered in all aspects of review design and conduct. Researchers should develop a “PICAR” statement to help form and focus on the research question(s) and eligibility criteria, assess CPG quality using a validated appraisal tool, and extract, analyze, and summarize data in a way that is cogent and transparent.

Conclusion: SRs of CPGs can be used to systematically identify, assess, and summarize the current state of guidance on a clinical topic. These types of reviews often require methodological tailoring to ensure that their objectives and timelines are effectively and efficiently addressed; however, they should all meet the criteria for an SR, follow a rigorous methodological approach, and adhere to transparent reporting practices. © 2018 Elsevier Inc. All rights reserved.

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1. Background

Clinical practice guidelines (CPGs) are organized clinical statements designed to assist practitioners with health care decision-making [1]. Numerous CPGs exist on a range of topics; however, not all are evidence-based or methodologically rigorous. Clinical consensus statements, for example, reflect synthesized opinions from an organized group of experts and aim to describe “customary and

expected care to be offered to patients” [2] in situations where little to no evidence is available [3]. In contrast, evidence-based CPGs are developed through a review of available evidence, report an explicit set of recommendations informed by that evidence, and typically include a formal assessment of the benefits and drawbacks of available treatment options [1,2].

In addition to their depth of evidence base and general methodologic quality, CPGs can vary in a variety of other ways, such as clinical orientation/focus and purpose, complexity of presentation, format, and intended end-users [4]. Indeed, the nature and breadth of recommendations reported across CPGs can also vary substantially. Recognizing this diversity, systematic reviews (SRs) of CPGs are becoming increasingly popular knowledge synthesis activities through which researchers attempt to systematically characterize the nature of clinical guidance on a topic of interest.

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What is new?**Key findings**

- Systematic reviews (SRs) of clinical practice guidelines (CPGs) are unique knowledge syntheses that require tailored approaches to, and greater subjectivity in, design and execution compared with other SRs in clinical epidemiology.

What this adds to what was known?

- This is the first methodological guidance article specifically focused on the design and conduct of SRs of CPGs. It addresses the paucity of guidance for these types of literature syntheses and contributes to the existing literature based on SR methodology.

What is the implication and what should change now?

- The unique characteristics of CPGs/guideline recommendations as research syntheses/clinical guidance statements and the clinical and geographical context within which these types of reviews are carried out must be considered during all stages of review design and conduct. We recommend that authors adopt the guidance outlined in this article when designing and executing their own SR of CPGs.
- The guidance outlined in this article can be applied to SRs of guidelines developed for use outside clinical medicine, such as those used in the fields of public health and social care.

Although many published reviews of CPGs are referred to as “systematic,” the scientific rigor with which they are conducted varies, and many use methods that are neither fully systematic nor reproducible [5]. Furthermore, their reporting practices vary widely, likely owing to a paucity of methodologic guidance for these specific types of knowledge syntheses. In this article, we fill this knowledge gap by providing structured guidance to review authors who wish to conduct a methodologically rigorous SR of CPGs.

1.1. SRs of CPGs

There are several scientific and practical reasons for conducting SRs of CPGs; however, they are generally conducted to identify gaps in knowledge about the current state of clinical guidance on a particular issue. Similar to all SRs, the core components of SRs of CPGs include a precise clinical question, a reproducible search strategy that aims to identify all relevant literature, explicit inclusion criteria, a critical appraisal of included literature, and a transparent summary of findings [6–12]. If one of these key elements is missing, the study should be distinguished appropriately

from a “systematic” review (e.g., a “survey” of CPGs or guideline recommendations [CPGRs]). Although not necessary, when appropriate, some SRs of CPGs may wish to use any of a variety of rigorous techniques to aggregate or “meta-synthesize” CPGRs (and other relevant qualitative data) reported across CPGs [13–15].

Similar to other SRs [6–12], well-designed and rigorously executed SRs of CPGs can provide high-levels of evidence for decision-making. As shown in Table 1, the rationale and specific aims of such reviews can vary substantially across studies; however, they can be broadly distinguished by their principal focus, that is, CPGs or CPGRs, which we will refer to from this point forward as distinct, yet inextricably linked, “units of analysis.”

2. Suggested methodology for SRs of CPGs*2.1. General considerations*

The rationale for conducting SRs of CPGs is frequently context-specific; thus, their design and conduct require certain considerations that may not be applicable to other types of reviews. For example, SRs of CPGs commonly aim to inform a specific national, regional, or local context. As such, it may be appropriate to limit guideline eligibility to a specific publishing body/region of origin to ensure that the findings are in the correct clinical context. Indeed, as outlined in Table 2, various other types of “methodological tailoring” may be necessary to ensure that review objectives and timelines are effectively and efficiently addressed. These constraints may not necessarily constitute “rapid review” [31–34]; however, any type of methodological tailoring or constraint on CPG/CPGR inclusion should be justified, considered a priori, and have minimal impact to study rigor and validity.

2.2. Develop an explicit, transparent protocol

As in any SR, syntheses of CPGs must aim to answer a clear, transparent, and structured research question [5]. The question should support the stated rationale and objectives for conducting the review and should be defined a priori in a protocol. The protocol should outline the review methodology by stage and be developed and agreed upon by all research stakeholders before the start of review. We suggest that protocols for SRs of CPGs be published [27] or registered in open-access sources (e.g., PROSPERO [35]) before the review begins. This encourages transparency, prevents research waste, and provides critical protocol review through established publication or registration processes.

2.3. Frame the research question and define the eligibility criteria

We advise using the “PICAR” framework to help form and focus the research question and define CPG and

Table 1. Rationale, aims, and objectives of recently published systematic reviews of CPGs^a

Clinical topic	Review rationale	Review aims and objectives
CPGs as the primary unit of analysis		
Traditional Chinese medicine (TCM) [16]	An increasing number of TCM CPGs are being developed; there is a need to assess their quality	To assess the quality of TCM CPGs to inform and improve their development in the future
Kidney transplantation [17]	The quality of CPGs is known to vary.	To determine the quality of UK-based CPGs on the topic.
Rehabilitation of moderate or severe acquired brain injury in children [18]	The quality of CPGs is known to vary, and previous reviews of guidelines on acquired brain injury have focused on adults only.	To appraise the quality of eligible CPGs focused on children. The authors also identified and synthesized specific recommendations of interest that were reported by included CPGs.
Cough [19]	The quality of guidelines on the topic varied.	To assess the quality of CPGs and identify gaps in evidence as reflected by the quantity and nature of recommendations they report.
CPGRs as the primary unit of analysis		
Patients with depression who have an inadequate response to first-line treatment with SSRIs [20]	Patients generally experience poor response rates to first-line antidepressants, and untreated depression can lead to negative consequences.	To critically evaluate CPGs on the topic. The authors appraised the quality of included CPGs and synthesized recommendations of interest.
Cancer evaluation of selection of solid organ transplant candidates [21]	A review of the current state of guidance on diagnostic tests for cancer, as part of the process of selecting candidates for solid organ transplants, would be useful to clinicians.	To investigate the nature of recommendations reported by eligible CPGs (availability, quality, and consistency). The authors also assessed the quality of included guidelines.
Dietary sugar intake [22] ^b	There are conflicting recommendations on the intake of dietary sugar, which raises concerns about guideline quality and the evidence supporting the recommendations reported in clinical guidelines on the topic.	To critically appraise the quality of guidelines reporting recommendations for dietary sugar intake. The authors assessed the evidence supporting the recommendations reported.

Abbreviations: CPGs, clinical practice guidelines; CPGRs, clinical practice guideline recommendations; SSRIs, selective serotonin reuptake inhibitors.

^a We have separated the reviews into two broad categories based on their primary unit of analysis (i.e., the author-reported primary outcome); however, it is important to note that the review's primary unit of analysis may not necessarily be reflected in its title. For example, some reviews may be titled SRs of CPGRs; however, these reviews are always, in essence, an SR of CPGs.

^b The units of analysis in this review were public health guidelines and recommendations as opposed to CPGs and CPGRs. The guidance provided in this article, however, is applicable to guidelines on topics outside clinical medicine.

CPGR eligibility criteria. This framework, pragmatically developed to guide internal SRs of CPGs at the University of Ottawa Heart Institute, is defined as: *P: Population, clinical indication(s), and condition(s), I: Intervention(s), C: Comparator(s), Comparison(s), and (key) Content, A: Attributes of eligible CPGs, and R: Recommendation characteristics*. This acronym is an adaptation of the PICO(T/S) statement for SRs of interventions and has been modified to meet the specific needs of SRs of CPGs [36].

The protocol should define the inclusion and exclusion criteria for each of the five elements in the PICAR statement, some of which will be more relevant than others at various stages of the literature search (Section 2.3.1) and inclusion screening (Section 2.3.2) processes. Important considerations that should be made when developing a PICAR statement are outlined in Table 3. Note that Table 3 is separated into two columns (i.e., by an SR of CPGs' two units of analysis) for the purpose of

explanation only. Each study PICAR should be created as a single statement.

2.3.1. Identify relevant CPGs: the literature search

Searching for CPGs requires a multi-tiered approach, and we recommend consulting with an experienced information specialist or librarian to design and/or execute the search strategy. Many CPGs are published in journals and can be identified through systematic bibliographic database searching; however, others may only be published in noncommercial or proprietary formats and are accessible only through extensive searches of gray (unpublished) literature sources. Furthermore, some professional medical associations will post CPGs on their websites behind membership paywalls. Specific search parameters, including publication dates, region of origin, or jurisdiction of the CPG producer, and any limitations to the search that may be applied should be fully considered before the execution of the search. For additional guidance on the

Table 2. Examples of various types of methodological tailoring applied in published SRs of CPGs^a

Type of restriction	Examples	Rationale for using the restriction
Language	Non-English language/English-translated CPGs were excluded [19–21,23,24].	No explicit rationale provided; discussed as a limitation [19–21,23].
Year of publication	Literature searches, and/or included CPGs, were restricted to records published after a specific year [20,23–25].	Authors were only interested in recently published CPGs [20,23,25].
Region of origin	Supplemental guideline searches were restricted to societies of first-world countries and the largest second- and third-world countries [26].	Limitation was implemented for “feasibility reasons” [26].
Publishing body	Only CPGs issued or endorsed by national or international scientific societies and government organizations were included [23,25].	Authors considered “patient and allied health professional guidelines and technical guides” as “non-CPG documents” [23].
Scope	CPGs were excluded if they were not “national in scope” [20].	No explicit rationale provided; discussed as a limitation [20].
Inclusion screening and data extraction	CPGs were screened for inclusion in “blocks” by publication year (being with those most recently published). When ≥ 1 CPG was deemed fully eligible within each publication year block, data extraction was immediately completed. This process continued until saturation was reached [27].	Only the most recent CPGs and CPGRs were of interest to the review sponsor [27].
	CPGs with fewer than three authors were excluded [23].	No explicit rationale provided [23].
	Documents with “medical algorithms with no background or description of the process by which the algorithm was developed” were excluded [20].	The authors did not recognize medical algorithms as CPGs [20].
Methodological quality	CPGs published in “other forms (e.g., books, booklets, government documents)” were excluded [19].	No explicit rationale provided; discussed as a limitation [19].
	Recommendations were extracted by a single author and independently reviewed for accuracy by another [23,24].	No explicit rationale provided [23,24].
	Further consideration of otherwise eligible CPGs was limited to those assessed a specific minimum quality cut-off score, e.g., a score of $>40\%$ and $\geq 70\%$ in AGREE II Domain 3 [28,29] or a score of $\geq 60\%$ in AGREE II Domains 1, 3, and 6 [30].	Authors defined CPGs meeting specific cut-off scores as “high quality” [30] or “high priority” [28] for further consideration/review.

Abbreviations: AGREE II, the Appraisal of Guidelines for Research and Evaluation Instrument version 2; AGREE II Domain 1, scope and purpose; Domain 3, rigor of development; Domain 6, editorial independence; CPGs, clinical practice guidelines; CPGRs, clinical practice guideline recommendations; SRs, systematic reviews.

^a This list should not be considered exhaustive. Furthermore, as previously stated, some review authors refer to their studies as SRs of CPGRs; however, all SRs of CPGRs are, in essence, also SRs of CPGs.

conduct of literature searches for SRs of CPGs, see [Appendix 1](#).

2.3.2. Identifying relevant literature: screening CPGs and CPGRs for inclusion

A systematic and iterative approach to literature screening should be used to ensure that relevant CPGs and CPGRs (if applicable) are selected for inclusion. A minimum of two screening stages should be used to systematically apply the criteria defined in the PICAR

framework to each record retrieved, and each stage should involve two independent reviewers.

2.3.2.1. Identifying eligible CPGs. First, the titles and abstracts of all records retrieved from the literature search should be screened to exclude records that are overtly not of interest. Caution is warranted when applying inclusion criteria too explicitly during initial screening stages, especially if individual recommendations are of interest. Reviewers may wish to initially apply each element of the

Table 3. Elements of the PICAR statement of relevance to CPGs and CPGRs^a

PICAR item	PICAR items relevant to screening CPGs for inclusion	PICAR elements relevant to screening CPGRs for inclusion ^b
P: Population, clinical indication(s), and condition(s)	<p>Study population: e.g., age, sex, gender, nationality, race, hospitalization status.</p> <p>Clinical indication: e.g., treatment or prevention of disease X (in general or specific scenarios); patients requiring X intervention.</p> <p>Clinical condition: e.g., disease or condition X.</p>	All elements of the study population, clinical indications, and conditions that are relevant to the inclusion of CPGs (aside) are also applicable to the inclusion of CPGRs.
I: Intervention(s)	<p>All interventions are of interest: Reviewers should state “any intervention.”</p> <p>Specific intervention(s) is/are of interest: If CPG eligibility will be restricted to those that discuss a specific intervention (or interventions) of interest (e.g., a drug class, medication, surgery, program, or diagnostic test), a list of eligible interventions must always be provided. Authors must also be explicit about <i>where</i> screeners should look for this information. For example, authors may choose to screen CPGRs against this criterion and include all CPGs that report at least one CPGR on their intervention of interest. In these cases, the “R” portion of the PICAR must provide a statement to this effect.</p>	<p>All interventions are of interest: If all CPGRs reported by eligible CPGs are of interest, reviewers should state “any intervention.”</p> <p>Specific intervention(s) is/are of interest: If CPGR eligibility will be restricted to those that discuss a specific intervention of interest, each CPGR will have to be individually screened for inclusion against a list of eligible interventions (see examples aside). A full list of interventions must be listed here.</p>
C: Comparator(s), comparison(s), and (key) content	<p>All comparators and comparisons are of interest, and no “key” CPG content will be considered: Reviewers should state “any comparator or comparison. No ‘key’ CPG content is of interest.”</p> <p>Specific comparator(s) or comparison(s) is/are of interest: If CPG eligibility will be restricted to those that compare intervention X with alternative treatments Y and Z (comparators); authors must be explicit about where screeners should look for this information. If CPGRs will be screened for this purpose, the “R” portion of the PICAR must provide a statement to this effect. A list of eligible comparators/comparisons must always be provided.</p> <p>(Key) Content is of interest: If CPG eligibility will be restricted to those that contain “key” content of interest (e.g., CPGs that discuss sex/gender differences in the treatment of disease X), authors must be explicit about <i>where</i> screeners should look for this information. If CPGRs will be screened for this purpose, the “R” portion of the PICAR must provide a statement to this effect. A clear definition of the content of interest must always be provided.</p>	<p>All comparators and comparisons are of interest: If all CPGRs reported by eligible CPGs are of interest, reviewers should state “any comparator/comparison” (note that this will also include “none”).</p> <p>Specific comparator(s) or comparison(s) is/are of interest: If reviewers are only interested in CPGRs that discuss specific comparators/comparisons (e.g., “We recommend the use of intervention X over comparator Y” where Y can be any pharmaceutical agent but <i>not</i> behavioral interventions), individual CPGRs will have to be individually screened for inclusion against a list of eligible comparators/comparisons. A list of eligible comparators/comparisons must always be provided.</p> <p>(Key) Content is of interest: If reviewers are only interested in CPGRs that discuss key content (e.g., sex-specific CPGRs), individual CPGRs will have to be individually screened for inclusion for those that contain the specific content of interest. A clear definition of the content of interest must always be provided.</p>
A: Attributes of the CPG	Examples include CPG eligibility based on: Publication year (e.g., 2015 to present); language of publication; publishing or sponsoring organization; scope (e.g., national or international); clinical orientation/focus (e.g., broad or narrow); purpose (e.g., screening, prevention, diagnosis, treatment); format (e.g., CPGRs)	Not applicable

(Continued)

Table 3. Continued

PICAR item	PICAR items relevant to screening CPGs for inclusion	PICAR elements relevant to screening CPGRs for inclusion ^b
R: Recommendation characteristics and “other” considerations	<p>presented as text, algorithms, in decision paths or in tables); specific methodological standards (e.g., searched ≥ literature databases); intended end-user (e.g., practitioners or patients); type of CPG (evidence-based or CCS); minimum quality score (e.g., AGREE II cut-off scores)</p> <p>Recommendations are not of interest: This item should be marked “not applicable” if CPG eligibility will not depend on the nature of CPGRs they report.</p> <p>CPG eligibility is dependent on the presence of eligible CPGRs: If CPGs are only eligible for inclusion if they report at least one CPGR of interest, authors must make a statement to this effect. Specific criteria about the sampling unit and any other eligibility criteria of importance (see aside) must also be provided.</p>	<p>Define the sampling Unit: e.g., eligible CPGRs include individual standalone statements (sometimes in bold or in bullet-form) with an associated level and/or grade of evidence. Authors should make clear <i>where</i> reviewers can locate eligible CPGRs (e.g., anywhere the main CPG text, presented separately in tables, in decision algorithms, or decision paths).</p> <p>“Other” eligibility criteria: e.g., CPGRs must only be extracted from a specific set of CPGs, such as those achieving a prespecified quality score cut-off (specified a priori). Other criteria may include limiting extraction to CPGRs informed by a minimum level of evidence (e.g., GRADE level B or higher). All such criteria should be predefined.</p> <p>“Other” considerations: e.g., CPGRs that discuss the duration of intervention X are of interest; however, CPGRs concerning laboratory monitoring of intervention X are <i>not</i> of interest</p>

Abbreviations: AGREE II, the Appraisal of Guidelines for Research and Evaluation Instrument version 2; CCS, clinical consensus statement; CPG, clinical practice guideline; CPGRs, clinical practice guideline recommendations.

In some cases, CPGR eligibility screening will only continue until at least one eligible recommendation is of interest is identified. In other cases, all CPGRs will have to be screened for eligibility and those deemed eligible, extracted.

^a These suggestions are not meant to be exhaustive.

^b CPGs and CPGRs are inextricably linked; that is, they cannot be considered distinct entities. Indeed, it is likely not possible to make judgments on CPGR eligibility by looking at recommendations in isolation from the CPGs in which they are reported. Reviewers may have to confirm their eligibility by referring to the CPG section within which they are reported to gain adequate context for making a judgment. This is especially important if a specific population, indication, or condition is of interest, and the CPG is broad in scope.

PICAR framework broadly to ensure that relevant CPGs (and CPGRs) are not overlooked. Some CPGs may not provide a structured abstract, so potentially relevant records should be passed on to the second screening stage where the full text of the record is obtained and screened for inclusion. This may result in a large number of records requiring full-text review, and additional resources or time may be required to complete this task. For reviews that are time sensitive, a more rigid screening process may be preferred. SR software [37,38] can facilitate an efficient and organized screening process.

2.3.2.2. Identifying eligible CPGRs. For SRs that aim to identify specific recommendations within CPGs, a third stage of eligibility screening is required. At this stage, the PICAR framework (especially the criteria identified in the “R” item) should again be applied but to each

recommendation reported. If a criterion of CPG inclusion is the presence of at least one recommendation of interest, the third stage of screening should be undertaken as soon as the CPG meets all other elements of the “PICAR” statement. If CPGs are included regardless of the recommendations they report, we suggest waiting to screen individual recommendations for inclusion *just* before the final data extraction process.

2.3.3. Identifying relevant literature: searching for CPG companions

Once the final set of included CPGs has been obtained, it is important to retrieve all associated companion articles (e.g., methodology supplements) before data extraction or quality assessment is undertaken. If links to these documents are not provided in the included CPG, formal supplementary searches may be required to locate them. All documents

collected should be verified independently by the review team to confirm completeness and to ensure that companions are appropriately matched. Care should also be taken at this stage to ensure that the latest version of each included CPG has been included, and none is present in duplicate.

2.4. Quality assessment

Low-quality CPGs can be ineffective and result in poor patient outcomes if they disseminate recommendations based on information that is incomplete or scientifically inaccurate [39]. Each included CPG should, therefore, be assessed for quality using a validated tool designed for this purpose. In 2013, Siering et al. [40] identified and compared the content of 40 different guideline appraisal tools, which differed in terms of the number of items and breadth of dimensions covered. The authors found that most tools could be classified as (1) general instruments with either no or few actual appraisal criteria, (2) tools with specific questions/appraisal criteria, and (3) tools with specific questions/appraisal criteria that also require assessor judgments. Although most tools across all categories focus on CPG methodology and not necessarily clinical content, instruments in category 3 also require that appraisers judge the appropriateness of the methodology used [40].

The choice of appraisal tool should depend primarily on the SR's aims and objectives [40], and validated tools should be prioritized. For example, if the review's focus is CPG implementability, Siering et al. [40] suggest that the Guideline Implementability Appraisal tool (GLIA Version 2.0) [41] be used. For those who wish to perform a comprehensive appraisal of CPGs, Siering et al. suggest the use of Appraisal of Guidelines for Research and Evaluation Instrument version 2 (AGREE II) [42] or the German Instrument for Methodological Guideline Appraisal (DELBI) tool [43]. Of these, AGREE II is the most widely used and prolifically cited in the literature [44–47]. Given the popularity of this tool, we provide further guidance on its use in [Appendix 2](#).

Although no validated quality appraisal tool for CPGRs currently exists, the AGREE Recommendations Excellence (AGREE- REX) instrument, which is currently in the late stages of development, may be used to assess the “clinical credibility and implementability of guideline recommendations” [48,49] in future reviews. Furthermore, as CPGs typically present each recommendation with an associated strength (e.g., strong recommendation) and level of evidence (e.g., GRADE IA), review authors may wish to interpret these items as one form of CPGR quality. We caution reviewers, however, in interpreting or “ranking” the quality of recommendations strictly on the basis of the evidence used to inform them. Indeed, many clinically important recommendations are formed on the basis of very limited evidence and not every CPGR that has been informed by high-quality evidence will result in successful outcomes in every case [50].

Reviewers may aim to only include, or restrict data synthesis to, higher quality CPGs; however, the pros and cons of this approach should be carefully considered. For example, conclusions about the quality of individual CPGs may differ depending on the assessment tool used. Furthermore, guidelines determined to be of “high quality” may not necessarily report recommendations that are highly valid and implementable [51]. If these types of restrictions are made, they must be justified, explicitly defined in the PICAR statement, and specified a priori in the study protocol.

2.5. Data extraction and analysis

Ideally, data extraction should be completed in duplicate by two independent reviewers; however, if not practical, it may still be appropriate to have one reviewer extract data, and another independently verify the results for accuracy and completeness. The research question and review objectives should guide data extraction, and all data analyses should be carried out using rigorous processes that facilitate transparency of reporting.

2.5.1. Extracting and analyzing data from CPGs

The general characteristics of included guidelines, such as title and year of publication, name and location of publishing organization, range of topic(s) addressed, PICAR elements, and intended audience are a suggested minimum set of data that should be extracted. SR software [37,38] can facilitate an efficient and organized data extraction process. If CPGRs are of interest, further extraction, analysis, and synthesis will be necessary (see [Section 2.5.2](#)). Descriptive analyses can be quite useful in helping reviewers organize, characterize, and interpret data extracted on CPG characteristics and the results of CPG quality assessments.

2.5.2. Meta-synthesizing CPGRs

CPGRs can be challenging to meta-synthesize (i.e., extract, analyze, and synthesize) for several reasons. First, the number of recommendations of interest may be extensive and, given their qualitative nature, data extraction and management may be cumbersome. Second, CPGRs that are similar in overall focus may differ with respect to specific details, use slightly different terminology, discuss different interventions/comparators, and the systems applied to assess the quality of evidence behind them can vary substantially across CPGs [52]. For these reasons, reviewers must use systematic methods to complete these processes in a manner that maximizes efficiency.

With efficiency in mind, the choice of synthesis technique(s) should be driven by the review's aims and objectives [15,53,54]. Once these are established, we suggest that reviewers identify key features of recommendations that need to be extracted and analyzed to address the study's research question(s). These “elements” will be

the focus of their data synthesis. For example, if the study aims to compare the *levels of evidence supporting CPGRs* reported across included CPGs, the quality of evidence underpinning each extracted recommendation would be of key importance. Characteristics such as these can be collected through the construction of a recommendation matrix, that is, a table that specifies all elements by which recommendations will be characterized and summarized [55,56]. Some important characteristics will be definable a priori, whereas others might only be evident once data are extracted (e.g., differences in CPGR content based on factor “x”); thus, the matrix may evolve over time. An example recommendation matrix used in our own SR of CPGs is provided in Table 4.

CPGs may use more than one evidence assessment system, making comparisons across recommendations difficult. Indeed, evidence rated as “moderate quality” using one instrument could be rated as “low quality” by another [60–62]. If comparisons of this sort are of interest, we recommend that researchers create an evidence matrix (i.e., a review-specific evidence grading scheme) and standardize the levels of evidence associated with each CPGR to aid with data analysis and final data synthesis processes [21,63]. To create such a matrix, reviewers should first familiarize themselves with the assessment systems of

CPGs from which recommendations were extracted to gain an overall sense of the nature of classifications used. Evidence categories can then be developed using an iterative process of refinement (e.g., are the evidence categories too broad or narrow?) and testing (e.g., can the system be applied to recommendations reported by all CPGs?), in discussion with the review team.

In some cases, it may be feasible to build a recommendations matrix using SR software or other tools (e.g., spreadsheet or word processing software), extract CPGRs directly into the matrix, use the table to organize and sort the data according to meaningful categories, and quickly analyze the data it summarizes using descriptive statistics. Many SRs of CPGs, however, aim to further characterize guideline recommendations in a manner that requires the use of techniques that may not be feasible to use within the confines of a recommendations matrix, especially if a large number of CPGRs are of interest. For example, some reviews may aim to assess CPGRs for consistency and identify content gaps or emergent themes associated with recommendation content. In these instances, we recommend review authors extract and analyze the content of CPGRs, simultaneously, outside the recommendations matrix. Once completed, the results of such analyses can then be summarized within the matrix, when appropriate.

Table 4. Example recommendation^a matrix used in an SR of CPGs completed by researchers at the University of Ottawa Heart Institute

Indication: prevention of DVT in breastfeeding women					
Source CPG	CPG quality ^b	Recommendation	Standardized level of evidence ^c	Comparative treatment preference	Agent or drug class mentioned
Bates et al. (2012) [57]	High quality	“For breastfeeding women, we suggest alternative anticoagulants rather than fondaparinux (Grade 2C).”	Level C	Fondaparinux is not preferred; no comparator	FDP
Cardiovascular Disease Educational Research Trust et al. (2013) [58]	Moderate quality	“Breastfeeding is not contraindicated with either LMWH, LDUH, or warfarin (level of evidence: low).”	Level B	No	LMWH
James et al. (2011) [59]	Low quality	“Because warfarin, LMWH, and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant, these anticoagulants are compatible with breastfeeding” [“recommendation and conclusion... based on limited or inconsistent scientific evidence (Level B)”].	Level C	No	LMWH

Abbreviations: CPG, clinical practice guideline; DVT, deep vein thrombosis; FDP, fondaparinux, LMWH, low molecular weight heparin; LDUH, low-dose unfractionated heparin; SRs, systematic reviews.

^a Although termed a “recommendation matrix,” some characteristics of the CPGs from which they were extracted may also appear (e.g., CPG quality assessment scores).

^b High quality = CPGs that scored $\geq 60\%$ in at least three of six AGREE II domains, including Domain 3; moderate quality = CPGs with three AGREE II domains assessed a score of $\geq 60\%$, except Domain 3; low quality = CPGs that scored $< 60\%$ in two or more domains and scored $< 50\%$ in Domain 3.

^c Level B = moderate quality evidence (e.g., systematic review of cohort studies; at least one well-conducted cohort study; at least one lower quality randomized controlled trial); Level C = low-quality/limited evidence (e.g., case series; poor-quality cohort studies; a systematic review of case–control studies; other type of experimental study).

If researchers aim to summarize the frequency of occurrence of CPGR categories (e.g., the number of recommendations reporting on disease prevention vs. treatment), a content analysis approach to extraction and analysis is suggested. If reviewers wish to identify overarching themes associated with CPGRs of interest, thematic analysis can also be used [55,64–66]. Qualitative data analysis software (e.g., Nvivo [67]) will be quite useful in facilitating the collection, organization, analysis, and final summarization of findings for this purpose. Using this software, reviewers can screen CPGs for recommendations of interest, select relevant text, and assign a code to each sampling unit in a manner consistent with best practices in qualitative analysis methodology [64]. Once all relevant CPGRs have been identified and coding is complete, the software enables the final dataset to be efficiently sorted and organized.

2.6. Summarizing review findings

The structure of the final research summary (i.e., report or manuscript) will vary depending on the review objectives and scope, intended audience, and the technical

specifications of the sponsor or journal. Most summary documents include an introduction to the topic and study rationale, followed by a description of the methods used to conduct it. Because literature screening, selection, and data extraction/analyses are often tailored and review-specific, they must be transparently and comprehensively reported. A structured summary of findings should also be provided, after which reviewers should explain their meaning in a discussion [68]. The review's strengths and limitations should also be articulated. Although no checklist of reporting items was designed specifically for SRs of CPGs, we recommend authors make use of existing checklists, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [69] or guidelines for reporting meta-epidemiological research [70], which will be helpful in ensuring that key elements of the review are summarized. A completed copy of any checklist used should be included as a supplement.

All reviews should incorporate a narrative synthesis of results, to some degree, in their final summary of findings. We suggest that reviewers narratively summarize the results of the literature search and screening processes in a clearly

Study-Specific Criteria	
Population & clinical indications	<ul style="list-style-type: none"> • Adult (>18 years) outpatients • 10 clinical indications
Interventions	<ul style="list-style-type: none"> • Low molecular weight heparin (LMWH; individual agents and drug class) • Fondaparinux (FDP)
Comparators	<ul style="list-style-type: none"> • No comparator; any antithrombotic pharmaceutical agent; individual LMWH agents compared head-to-head; FDP compared to LMWH (drug class or individual agents)
Attributes of eligible CPGs	<ul style="list-style-type: none"> • Language: Available in English • Year: published ≥2005 • Publishing region: North America, Europe, Japan, Australia, & New Zealand • Version: Latest version only • Development process: Must be explicitly evidence-based • System of rating evidence: Must use a system to rate the level of evidence behind recommendations • Scope: Must have a primary focus on the management of VTE and/or DVT • Recommendations: At least one eligible recommendation is reported
Recommendation characteristics	<ul style="list-style-type: none"> • Duration of treatment: Recommendations on duration of treatment with LMWH/FDP are of particular interest • Levels of confidence: Each recommendation must be accompanied with an explicit level of confidence (e.g., GRADE 2A) • Interventions: Recommendations must explicitly discuss ≥ 1 intervention of interest • Comparators: Recommendations are not required to compare an intervention of interest to another antithrombotic agent. If such a comparison is made, the comparator must also meet specific eligibility criteria (see <i>comparators</i>) • Locating recommendations: within CPG text, tables, algorithms, and/or decision paths

Fig. 1. “PICAR” statement of an SR of CPGs conducted by researchers at the University of Ottawa Heart Institute. CPGs, clinical practice guidelines; SRs, systematic reviews.

constructed flow diagram such as that described by the PRISMA working group [69]. A narrative synthesis of CPG characteristics should also be provided as a standalone table in the main report. If the table is unacceptably large, this information can be summarized in the main text and a detailed table provided, instead, as an appendix. The final report should also summarize CPG (and CPGR, if applicable) quality assessment scores. Regardless of the summary method (e.g., table or figure), raw scores should be provided as supplemental information for the purposes of transparency.

For reviews focused on CPGRs, the results of all meta-syntheses should be summarized; however, the manner in which way these results are presented depends on the

review objectives, type(s) of technique(s) used, as well as the quantity of data extracted. If there are few included recommendations, reviewers may wish to present their recommendation matrix as a standalone table within the final report and narratively contextualize the information reported. If the number of recommendations is extensive, this information will likely need to be summarized in the main text and the full table reported in an appendix. Any findings that may be inappropriate or difficult to summarize in the recommendations matrix should be presented separately (e.g., a detailed summary of the results of content analyses or key findings of thematic analyses) in a manner that is useful and understandable to the target audience [71].

Table 5. Methodology used to conduct an SR of CPGs by researchers at the University of Ottawa Heart Institute

Background: In Ontario, low molecular weight heparins (LMWHs) and fondaparinux (FDP) are available through the Ontario Drug Benefit (ODB) formulary; however, they are only accessible through the limited use (LU) benefit and Exceptional Access Program (EAP). Prescribers have described this mixed LU/EAP listing as confusing and burdensome as these medications are covered under a variety of different codes and criteria for several indications. Prescribers have also noted evidence to support their use for indications not listed on the ODB. To help modernize the provincial formulary on the outpatient use of anticoagulant therapy, we completed an SR of CPGs on the recommended use of LMWHs and FDP across 10 clinical indications as part of an Ontario Drug Policy Research Network (ODPRN) drug class “rapid response” review. Our research protocol was peer-reviewed and published online before the start of review.

PICDR statement: Each element of the PICDR statement is outlined in Fig. 1.

Literature search: An experienced information specialist designed and executed the literature search strategy. CPGs were identified from Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, and the Cochrane Library. Gray literature was also searched using CADTH’s Gray Matters Light.

Screening for inclusion: A multi-tiered screening approach was used and facilitated using DistillerSR and a pilot test was successfully completed.

CPGs: Two reviewers independently screened all titles/abstracts for inclusion (*tier-one*). Full-text screening (*tier-two*) was completed by two independent reviewers in distinct blocks by descending year of publication. No full text published before 2011 was screened for inclusion, and CPGs were not excluded on the basis of overall quality. **Recommendations:** Two reviewers independently screened the full texts of otherwise eligible CPGs for the presence of eligible recommendations (*tier-three*). To be included, CPGs must have reported at least one recommendation of interest. Disagreements were resolved through consensus or involvement of a third reviewer.

CPG inclusion list: One reviewer searched for supporting documents (e.g., methodology supplements) of included CPGs. The completeness of each document set was independently verified by another reviewer. Two reviewers confirmed that the latest version of the CPG was included.

Data extraction: DistillerSR was used to facilitate data extraction, which was completed by one reviewer and independently verified for accuracy by another. Data extraction was completed immediately after ≥ 1 CPG was deemed fully eligible within each publication-year block (e.g., all CPGs published in 2016). One reviewer extracted all eligible recommendations from each CPG and assigned a general theme (e.g., pregnant women) to each. Details of the originating CPG’s evidence rating scheme were also extracted. Another reviewer independently reviewed the list of recommendations and rating schemes for accuracy and completeness. Disagreements were resolved through consensus.

Quality assessment: The AGREE II tool was used to assess the quality of included CPGs. Each domain assessed a score $\geq 60\%$ was considered effectively addressed. CPGs were considered “high quality” if they scored $\geq 60\%$ in at least three of six AGREE II domains, including Domain 3. If three domains or more were assessed a score of $\geq 60\%$, except Domain 3, they were considered to be of “moderate” overall quality. “Low-quality” CPGs scored $< 60\%$ in two or more domains and scored $< 50\%$ in Domain 3.

Recommendation meta-synthesis: First, we identified key elements that we felt should be the focus of data synthesis: (1) the levels of evidence underpinning recommendations, (2) the quality of CPGs from which they were extracted, (3) the frequency with which each anticoagulant class and individual agent was discussed, (4) comparative treatment preferences, and (5) emerging themes. Designed with these elements in mind, we created recommendation matrices (Microsoft Excel) for each indication to facilitate final data synthesis. More than one evidence assessment system was used by included CPGs; thus, we created a standardized evidence matrix and applied it to each recommendation. General themes associated with recommendation content were identified using thematic analysis.

Summarizing findings: We summarized our research findings in a structured report, and a manuscript of findings is currently in preparation. Briefly, the general characteristics of CPGs were narratively summarized, and the results of the AGREE II assessments were presented in a figure. Because of the large number of recommendations reported across CPGs, these data were summarized in tables by one reviewer and independently reviewed for accuracy and completeness by a second. We also summarized major recommendation themes (e.g., hip surgery, patients with cancer). Within each indication, we calculated the total number of recommendations reported, the frequency with which each anticoagulant class, and individual agents, were mentioned, and summarized the levels of evidence behind recommendations (from Level A, highest quality to Level D, expert opinion). We also investigated whether or not there was any apparent correlation between CPG quality and recommendation evidence (e.g., did high-quality CPGs mostly report Level A recommendations?). A full set of CPG characteristics, included recommendations, and raw AGREE II scores were provided as supplemental documents.

3. Methodological application: overview of a case exemplar

This article was informed by insights gained through our experience in conducting SRs of CPGs at the University of Ottawa Heart Institute [50]. To provide further context to the reader, we summarize the processes used to complete an SR of CPGs on the outpatient use of low molecular weight heparin and fondaparinux for 10 indications of importance to Ontario decision-makers in Fig. 1 and Table 5.

4. Conclusion

There are several scientific and practical reasons for conducting SRs of CPGs; however, they are generally conducted to identify gaps in, and summarize the current state of guidance on, a clinical topic. Compared with other SRs in clinical epidemiology, SRs of CPGs involve more subjectivity in design and execution and, thus, often require methodological tailoring to ensure that review objectives and timelines are effectively and efficiently addressed. In this article, we provided review authors with structured direction on the design and conduct of methodologically rigorous SRs of CPGs. Although there is no single acceptable approach to undertake such a review, they should all meet the criteria for an SR, follow rigorous methodological approaches, and adhere to transparent reporting practices. This guidance not only benefit researchers who require direction on conducting SRs of CPGs but will also be beneficial to review authors who require guidance on the design and conduct of SRs of guidelines developed for use outside clinical medicine such as those used in the fields of public health and social care.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jclinepi.2018.11.030>.

References

- [1] Clinical practice guidelines we can trust. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Washington, DC: National Academies Press (US); 2011.
- [2] Crosby E. Review article: the role of practice guidelines and evidence-based medicine in perioperative patient safety. *Can J Anesth* 2013;60(2):143–51.
- [3] Rosenfeld RM, Nnacheta LC, Corrigan MD. Clinical consensus statement development manual. *Otolaryngol Head Neck Surg* 2015;153(2 suppl):S1–14.
- [4] Guidelines for clinical practice: from development to use. In: Field MJ, Lohr KN, editors. Institute of Medicine (US) Committee on Clinical Practice Guidelines. Washington, DC: National Academies Press (US); 1992.
- [5] The Cochrane Collaboration. About Cochrane reviews: what is a systematic review?. Available at <http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html>.
- [6] Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015;13(3):132–40.
- [7] Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration. The Cochrane Collaboration; 2011. Available from: www.handbook.cochrane.org.
- [8] Gough D, Oliver S, Thomas J. *An introduction to systematic reviews*. Thousand Oaks, California: SAGE Publications; 2012.
- [9] Uman LS. Information management for the busy practitioner: systematic reviews and meta-analyses. *J Am Acad Child Adolesc Psychiatry* 2011;20(1):57–9.
- [10] Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. *J R Soc Med* 2003;96(3):118–21.
- [11] Godfrey C, Harrison M. Systematic review resource package. *Joanna Briggs Inst Reviewers' Man* 2015;4:30.
- [12] Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York, UK: University of York; 2009.
- [13] Dixon-Woods M, Agarwal S, Jones D, Young B, Sutton A. Synthesising qualitative and quantitative evidence: a review of possible methods. *J Health Serv Res Policy* 2005;10:45–53.
- [14] Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J* 2009;26: 91–108.
- [15] Korhonen A, Hakulinen-Viitanen T, Jylha V, Holopainen A. Meta-synthesis and evidence-based health care—a method for systematic review. *Scand J Caring Sci* 2013;27(4):1027–34.
- [16] Yao L, Chen Y, Wang X, Shi X, Wang Y, Guo T, et al. Appraising the quality of clinical practice guidelines in traditional Chinese medicine using AGREE II instrument: a systematic review. *Int J Clin Pract* 2017;71:1–8.
- [17] O'Donoghue KJM, Reed RD, Knight SR, O'Callaghan JM, Ayaz-Shah AA, Hassan S, et al. Systematic review of clinical practice guidelines in kidney transplantation. *BJS Open* 2017;1(4): 97–105.
- [18] Knight S, Takagi M, Fisher E, Anderson V, Lannin NA, Tavender E, et al. A systematic critical appraisal of evidence-based clinical practice guidelines for the rehabilitation of children with moderate or severe acquired brain injury. *Arch Phys Med Rehabil* 2018. pii: S0003-9993(18)30392-7.
- [19] Jiang M, Guan W, Fang Z, Xie Y, Xie J, Chen H, et al. A critical review of the quality of cough clinical practice guidelines. *Chest* 2016;150:777–88.
- [20] MacQueen G, Santaguida P, Keshavarz H, Jaworska N, Levine M, Beyene J, et al. Systematic review of clinical practice guidelines for failed antidepressant treatment response in major depressive disorder, dysthymia, and subthreshold depression in adults. *Can J Psychiatry* 2017;62(1):11–23.
- [21] Acuna SA, Lam W, Daly C, Kim SJ, Baxter NN. Cancer evaluation in the assessment of solid organ transplant candidates: a systematic review of clinical practice guidelines. *Transplant Rev (Orlando)* 2018;32(1):29–35.
- [22] Erickson J, Sadeghirad B, Lytvyn L, Slaviv J, Johnston BC. The scientific basis of guideline recommendations on sugar intake: a systematic review. *Ann Intern Med* 2017;166:257–67.

- [23] Kim JK, Chua ME, Ming JM, Santos JD, Zani-Ruttenstock E, Marson A, et al. A critical review of recent clinical practice guidelines on management of cryptorchidism. *J Pediatr Surg* 2018;53:2041–7.
- [24] Simons P, Cosgrove L, Shaughnessy AF, Bursztajn H. Antipsychotic augmentation for major depressive disorder: a review of clinical practice guidelines. *Int J Law Psychiatry* 2017;55:64–71.
- [25] Chiappini E, Bortone B, Galli L, de Martino M. Guidelines for the symptomatic management of fever in children: systematic review of the literature and quality appraisal with AGREE II. *BMJ Open* 2017;7(7):e015404.
- [26] Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal depression with antidepressants: an international review. *Aust N Z J Psychiatry* 2018;52(4):320–7.
- [27] Unit Ontario Drug Policy Research Network Systematic Review. Low molecular weight heparin: a review of clinical guidelines across indications 2015;5. Toronto.
- [28] Bush SH, Marchington KL, Agar M, Davis DHJ, Sikora L, Tsang TWY. Quality of clinical practice guidelines in delirium: a systematic appraisal. *BMJ Open* 2017;7(3):e013809.
- [29] Jakes AD, Marec-berard P, Phillips RS, Cantab MA, Oxon BM, Stark DP, et al. Critical review of clinical practice guidelines for fertility preservation in teenagers and young adults with cancer 2014;3(4):144–52.
- [30] Tonelli M, Conner Gorber S, Moore A, Thombs BD. Recommendations on routine screening pelvic examination. *Can Fam Physician* 2016;62:2014–7.
- [31] Mattivi JT, Buchberger B. [Rapid reviews: Sisyphos' salvation? - an inventory]. *Gesundheitswesen* 2017;79(5):438–42.
- [32] Tricco AC, Antony J, Zarin W, Strifler L, Ghassemi M, Ivory J, et al. A scoping review of rapid review methods. *BMC Med* 2015;13(1):224.
- [33] Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. *Syst Rev* 2012;1(1):10.
- [34] Kelly SE, Moher D, Clifford TJ. Defining rapid reviews: a modified Delphi consensus approach. *Int J Technol Assess Health Care* 2016;32(4):265–75.
- [35] Jolliffe L, Lannin N, Hoffmann T. Evidence-based rehabilitation interventions for adults with acquired brain injury: a systematic review of clinical practice guidelines to identify current best practice recommendations. York, UK: PROSPERO International prospective register of systematic reviews, University of York; 2016.
- [36] Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014;14:579.
- [37] DistillerSR. Ottawa, ON: Evidence Partners; 2018.
- [38] Covidence. London, UK: Cochrane; 2018.
- [39] Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Potential benefits, limitations, and harms of clinical guidelines. *BMJ* 1999;318:527.
- [40] Siering U, Eikermann M, Hausner E, Hoffmann-Eßer W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. *PLoS One* 2013;8:e82915.
- [41] Kashyap N, Dixon J, Michel G, Brandt C, Shiffman R. GLIA Guideline Implementability Appraisal V. 2.0. New Haven, CT: Yale University: Yale Center for Medical Informatics; 2011.
- [42] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182(18):1308–11.
- [43] German instrument for methodological guideline appraisal in deutsches instrument zur methodischen leitlinien-bewertung (DELBI). In: Kopp I, Thole H, Selbmann HK, Ollenschlaeger G, editors. Association of the scientific medical societies in germany and agency for quality in medicine. Available from: <https://www.leitlinien.de/medb/edocs/pdf/literatur/german-guideline-appraisal-instrument-delbi.pdf>.
- [44] Hoffmann-Eßer W, Siering U, Neugebauer EAM, Brockhaus AC, Lampert U, Eikermann M. Guideline appraisal with AGREE II: systematic review of the current evidence on how users handle the 2 overall assessments. *PLoS One* 2017;12:1–15.
- [45] The AC, Collaboration A. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;12:18–23.
- [46] Brouwers MC, Kerkvliet K, Spithof K. The AGREE reporting checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152.
- [47] Hoffmann-Eßer W, Siering U, Neugebauer EAM, Lampert U, Eikermann M. Systematic review of current guideline appraisals performed with the appraisal of guidelines for research & evaluation II instrument—a third of AGREE II users apply a cut-off for guideline quality. *J Clin Epidemiol* 2018;95:120–7.
- [48] Brouwers M, Florez ID, Spithoff K. Evaluating the clinical credibility and implementability of clinical practice guideline recommendations using the AGREE-REX tool. In: Global Evidence Summit. Cape Town, South Africa: Cochrane Colloquium Abstracts; 2017.
- [49] Brouwers MC, Team AGREE-REX Research. AGREE-REX: Recommendation EXcellence Application, AGREE-REX 2016. Available from: <http://www.agreetrust.org/wp-content/uploads/2016/01/AGREE-REX-Manual-Appl-testing.pdf>; McMaster University.
- [50] Johnston A, Hsieh SC, Carrier M, Kelly SE, Bai Z, Skidmore B, et al. A systematic review of clinical practice guidelines on the use of low molecular weight heparin and fondaparinux for the treatment and prevention of venous thromboembolism: implications for research and policy decision-making. *PLoS One* 2018;13:e0207410.
- [51] Watine J, Friedberg B, Nagy E, Onody R, Oosterhuis W, Bunting PS, et al. Conflict between guideline methodologic quality and recommendation validity: a potential problem for practitioners. *Clin Chem* 2006;52:65–72.
- [52] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck Y, Alonso-coello P, et al. Rating quality of evidence and strength of recommendations: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations rating quality of evidence of recommendations grade: of evidence an emerging and consensus of on rati. *Br Med J* 2008;336:924–6.
- [53] Finfgeld-Connett D. A guide to qualitative meta-synthesis. New York, NY: Taylor & Francis; 2018.
- [54] Mohammed MA, Moles RJ, Chen TF. Meta-synthesis of qualitative research: the challenges and opportunities. *Int J Clin Pharm* 2016;38(3):695–704.
- [55] Graham ID, Harrison MB. Evaluation and adaptation of clinical practice guidelines. *Evid Based Nurs* 2005;8(3):68–72.
- [56] Sprague AE, Oppenheimer L, McCabe L, Brownlee J, Graham ID, Davies B. The Ottawa hospital's clinical practice guideline for the second stage of labour. *J Obstet Gynaecol Can* 2006;28(9):769–79.
- [57] Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e691S–736S.
- [58] Cardiovascular Disease Educational Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology, Union Internationale du Phlebologie. Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence). *Clin Appl Thromb Hemost* 2013;19(2):116–225.
- [59] James A, Obstetrics Committee On Practice Bulletins. Practice bulletin no. 123: thromboembolism in pregnancy. *Obstet Gynecol* 2011;118(3):718–29.
- [60] Guyatt AD, Oxman, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, et al. What is “quality of evidence” and why is it important to clinicians? *BMJ* 2008;336(7651):995–8.

- [61] Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. *Health Res Policy Syst* 2006;4:1–7.
- [62] Hoffmann T, Bennett S, Del Mar C. Chapter 13- clinical practice guidelines. In: *Evidence-Based Practice Across the Health Professions*. Chatswood, NSW: Elsevier; 2017.
- [63] Team Members Abikus Project. ABIKUS Acquired Brain Injury Knowledge Uptake Strategy ABIKUS evidence-based recommendations for rehabilitation of moderate to severe acquired brain injury (2007) 2007. Available from: https://www.abiebr.com/pdf/abikus_aug_07.pdf.
- [64] Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res* 2005;15:1277–88.
- [65] Jolliffe L, Lannin NA, Cadilhac DA, Hoffmann T. Systematic review of clinical practice guidelines to identify recommendations for rehabilitation after stroke and other acquired brain injuries. *BMJ Open* 2018;8(2):e018791.
- [66] Bosch M, Tavender E, Bragge P, Gruen R, Green S. How to define 'best practice' for use in Knowledge Translation research: a practical, stepped and interactive process. *J Eval Clin Pract* 2013;19:763–8.
- [67] NVivo qualitative data analysis Software. Doncaster, VIC: QSR International Pty Ltd; 2012.
- [68] Hess DR. How to write an effective discussion. *Respir Care* 2004;49(10):1238–41.
- [69] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9. w64.
- [70] Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. *Evid Based Med* 2017;22(4):139–42.
- [71] G. Guest, K.M. MacQueen, and E.E. Namey. Writing up thematic analyses, in *Applied thematic analysis* 2012, SAGE Publications, Inc.: Thousand Oaks, CA. p. 241-278.