Journal of Clinical Epidemiology 116 (2019) 72−83

Journal of Clinical Epidemiology

REVIEW

Most guideline organizations lack explicit guidance in how to incorporate cost considerations

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Accepted 14 August 2019; Published online 17 August 2019

Abstract

Objectives: Resource use and cost (RUC) evidence is one of the factors that can be considered when formulating recommendations in clinical practice guidelines (CPGs). However, it is unclear how CPG developers incorporate this information. The purpose of this study was to identify available guidance from guideline organizations on how to incorporate RUC in CPGs.

Study Design and Setting: This is a methodological survey. We searched MEDLINE, the G-I-N library, the Cochrane Methodology Register, and gray literature from inception to 2017. We included the most recent version of guidance documents. We excluded those that only reported methodology for adapting, endorsing, or updating CPGs, and documents reporting methods followed in the development of one or more specific CPGs.

Results: We included 77 documents from 67 organizations. Fifty-nine organizations (88.1%) include information regarding RUC during the CPG development process. Fifty-five (82.1%) organizations report taking RUC into account when developing recommendations: 44 (65.7%) do this explicitly, 5 (7.5%) implicitly, and 6 (9.0%) explicitly as optional. Twelve of the 44 organizations that explicitly consider RUC (27.3%) provide guidance to identify, assess and use the RUC evidence when developing recommendations. Twenty-three consider RUC when moving from the evidence to recommendations (52.3%). Seventeen of the 44 (38.6%) recommend making qualitative judgments about whether the desirable effects of interventions were worth the associated costs.

Conclusion: More explicit guidance is needed alongside tools to help CPGs developers incorporate RUC evidence when formulating recommendations. Our results may be of use for guideline developers to improve this guidance.

Keywords: Guidelines; Guideline development; Methodology; Recommendations; Systematic reviews; Costs; Economic evaluations; Quality of the evidence; Certainty in the evidence

Disclaimer: The views expressed in this article are solely the authors' and do not reflect those of their professional affiliations. A.K. works for F. Hoffmann-La Roche Ltd but received no funding to prepare this article that is attributable to the manuscript.

Funding: This project was funded by a research grant from the Instituto de Salud Carlos III, Spain (FIS PI14/02,006 to Pablo Alonso-Coello). Pablo Alonso-Coello is funded by a Miguel Servet research contract from the Instituto de Salud Carlos III, Spain (CP16/00,137). Laura Martínez García is funded by a Juan Rodés contract from the Instituto de Salud Carlos III, Spain (JR15/00,004).

Conflict of interest: All the authors state they have no conflicts of interest with regard to the content of this article.

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https://doi.org/10.1016/j.jclinepi.2019.08.004

What is new?

Key findings

- Most guideline developers include, implicitly and/or explicitly, costs evidence in their guideline development process. However, the available guidance to identify, select, summarize, analyze, and use this information was generally limited and poorly described.

What this adds to what was known?

- Guideline developers are more aware of the relevance of introducing cost evidence when developing recommendations, but most of them are not explicit about the methods that need to be applied.
- The use of costs evidence in the guideline development process is complex and needs topic-specific expertise.

What is the implication and what should change now?

- Guideline developers need to be more explicit about the methods they use to consider costs evidence in guidelines. This would facilitate the user's interpretation of how this type of evidence influences recommendations.
- Guideline developers should provide enough guidance as they do for effectiveness evidence. At a minimum, this guidance should include the economic perspective used, the sources of information, the selection criteria of the evidence of costs, the methods used to rate its quality assessment, and how this information was used when moving from the evidence to recommendations.
- Evidence-based methodological guidance is needed on how to consider costs evidence in guidelines.

1. Introduction

Clinical practice guidelines (CPGs) have the potential to improve patient outcomes by facilitating appropriate practices in recommending effective therapies, reducing waste of resources and variability in health, and identifying gaps of knowledge and areas of research. CPGs provide an opportunity to review and update clinical pathways and to disinvest in obsolete technologies [1].

Alongside factors such as the balance between benefits and harms, equity, and feasibility, the resource use and cost (RUC) of the interventions may also influence recommendations in CPGs. Despite an increasing interest to incorporate RUC evidence into recommendations, the methods used by guideline developers have only been reviewed in one study to date, a review that included medical societies in the United States [2]. The review highlighted that the application of a systematic and explicit process to incorporate RUC evidence in guidelines is not yet systematic and is often ignored [2]. Given this context, we systematically reviewed CPG guidance documents, aiming to identify and describe the methods proposed by guideline developers to assess and incorporate RUC evidence into CPGs.

2. Methods

2.1. Data sources and searches

We report the results according to the PRISMA statement [3]. We conducted a systematic search in MEDLINE, via PubMed. In addition, we searched the databases of the Guidelines International Network (http://www.g-i-n.net) and the Cochrane Methodology Register. We searched in Google (www.google.com) and in organizations identified in previous works [4,5]. The searches were conducted from inception until December 2017. Language restriction to English was only applied in the Google search. The search strategy is available as Supplementary Data (Appendix 1).

2.2. Study selection

We included the last available version of documents (October 2018) that provided guidance on the development process of CPGs and were published in the last decade. We excluded guidance documents that only reported guidance for adapting, endorsing, or updating CPGs, and documents that described the methodology followed in the development of specific CPGs or a set of CPGs. Two reviewers independently selected potential guidance documents by reviewing titles and abstracts. They assessed the full text of those initially selected for their final inclusion. Disagreements were resolved by consensus or with the help of a third author.

2.3. Data extraction and quality assessment

Data were collected and managed through an electronic case report form (CRF) using the REDCap tool [6]. To develop the CRF, we first identified the main steps of the CPG development process and the areas relevant to RUC (Fig. 1). We extracted the following information: general characteristics of the organization; characteristics of the guideline development group (GDG); characteristics of conflict of interest management; incorporation of RUC evidence in the development of the CPGs (topic selection, scope, recommendations and implementation); strategy for prioritization of questions in which RUC implications should be considered; strategy to identify relevant RUC

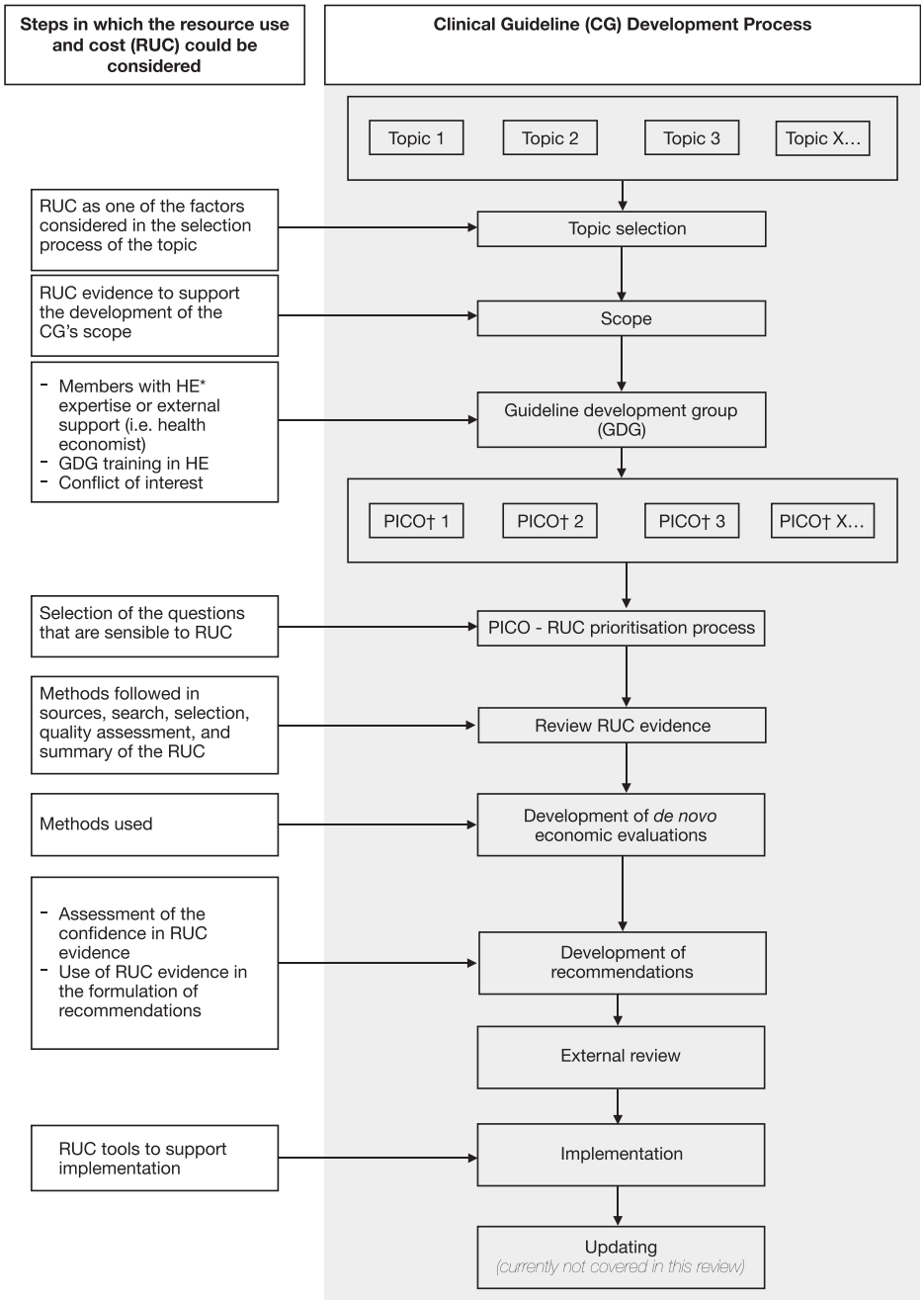

Fig. 1. Steps in which the resource use and cost could be considered during the clinical guideline development process. *HE: health economics, † PICO question format: Population, Intervention, Comparator and Outcome(s).

evidence; method to select and assess the relevance and the quality of this evidence; methods to develop de novo economic models; and methods to present this type of information and its integration into CPGs recommendations. We also extracted information about the economic impact of the recommendations during the development of the recommendation, when assessing the feasibility of the intervention, and/or during the development of implementation considerations (e.g., providing budget impact analysis or costing tools). One reviewer performed data extraction and another checked information accuracy. If a consensus was not reached, a third reviewer was consulted.

2.4. Analysis

We used descriptive statistics and calculated absolute frequencies and proportions for all items. We also conducted a narrative synthesis of the methods used by the organizations that explicitly considered RUC. Statistical analysis was performed using SPSS, version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

We examined the titles and abstracts of 7,920 references (Fig. 2). We selected 97 records for full-text examination and excluded 20 documents (Appendix 2). Finally, we included 77 documents, corresponding to 67 organizations (Appendix 3).

3.1. Organizations characteristics

Most of the guidance documents identified were developed by North American (30/67, 44.8%) [7−42] or European organizations (26/67, 38.8%) [43−68]. Most of the organizations included were either scientific societies (41/67, 61.2%) [7−9,11−28,30,32−34,36,39,40,43,45,46,49−54,58,59,63−65,67−69] or public organizations (20/67, 29.9%) [10,29,31,35,41,42,48,55−57,60−62,66,70−78] (Table 1).

3.2. Guideline development group composition

Sixteen organizations (16/67, 23.9%) stated that GDG members with experience in health economics (or health economists) should or could be members of the GDG, or be part of the technical team (Table 1) [21−23,48,56−58,61,62,64−66,70−72,74,76,78,79]. Seven organizations (7/67, 10.4%) described their role [21,22,48,57,62,74,76,79], with their tasks being mainly related to the review and the appraisal of economic literature, development of de novo economic evaluations, and budget impact analysis. Three organizations explicitly stated that they provided GDG members with training in introductory health economics, or that they provided this if necessary [48,57,62].

3.3. Development process

Fifty-nine organizations (59/67, 88.1%) reported considering RUC during the CPG development process (Table 2) [7−9,11,12,15−23,25,26,28−30,32−48,50−55,57−79,85−88]. Twenty-four organizations (24/67, 35.8%) considered RUC when prioritizing CPG topics [11,12,15,17−23,25,32,35,37,38,43,47,48,60,61,63,64,74−76,78,85], and for 13 organizations (13/67, 19.4%),

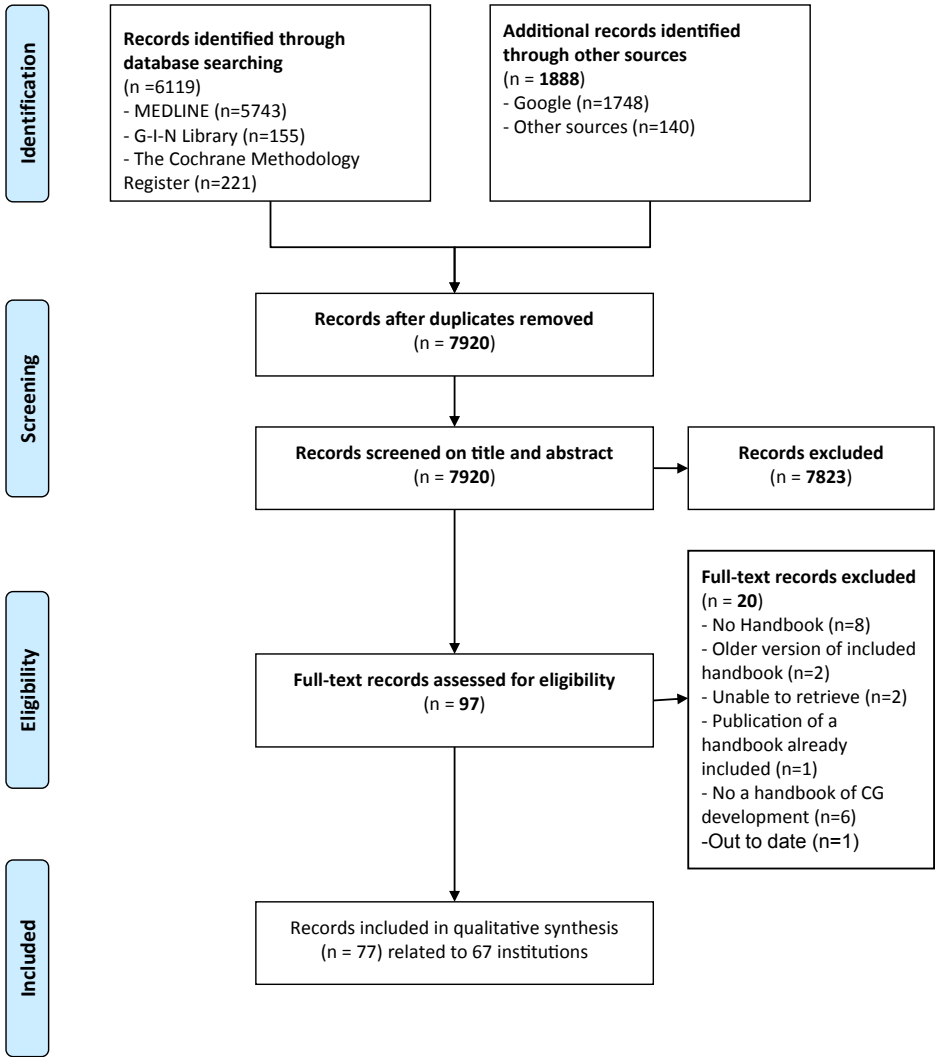

Fig. 2. Literature flow diagram.

Table 1. Clinical guideline organizations—general characteristics ($n = 67$)

General characteristics	Frequency	Percentage
Geographical location		
North America	30	44.8
Europe	26	38.8
Australia and/or New Zealand	4	6.0
Asia	3	4.5
South America	2	3.0
International	2	3.0
Type of organization		
Scientific society	41	61.2
Public organization	20	29.9
Other[a]	5	7.5
Private organization	1	1.5
Guideline development group composition		
Chair	62	92.5
Health care professionals	66	98.5
Patients and/or carer(s) member(s)	40	59.7
Technical members (methodological support)	45	67.2
Other[b]	22	32.8
Health economist[c]	16	23.9
Not reported	1	1.5
Conflict of interest reported		
Yes	65	98.5
No	2	3.0

[a] Nongovernmental or international organizations.
[b] Stakeholders, medical ethics experts, researchers.
[c] Person with experience in health economics.

RUC was one of the aspects to consider when developing the scope of a CPG [15,17,19,36,57,60,62,64,73,74,76,79,86−88]. Twenty-three organizations considered RUC when developing the CPG implementation strategies (23/67, 34.3%), mainly considering the resource implications [7−9,28,30,34,43,44,46,48,51,57,58,61−64,66−68,70−72,74,76,79,85].

Most organizations reported they considered (or could consider) RUC when formulating recommendations (55/67, 82.1%) (Table 2): 44 organizations (44/67, 65.7%) were explicit about the consideration of RUC, whereas five organizations (5/67, 7.5%) considered RUC implicitly (e.g., reporting the use the Grading of Recommendations, Assessment, Development and Evaluation [GRADE] approach when formulating recommendations but not providing details about the factors considered) [23,28,53,73,86−88], and six (6/67, 9.0%) considered RUC in the development of clinical recommendations as optional (Table 2) [7−9,16,21,22,25,46,52]. These six generally included a summary of the available economic evidence or developed additional recommendations including RUC (Appendix 4.1 RUC Optional).

3.4. Consideration of RUC in the development of recommendations

3.4.1. Prioritization of clinical questions sensitive to RUC

Nine of the 44 (9/44, 20.5%) organizations that explicitly stated in their guidance documents that they considered RUC in the development of their CPG recommendations recommended early identification of the most relevant clinical questions, that is, those which were likely to require a more detailed evaluation of their economic implications (i.e., requiring a systematic review [SR] of the available economic evidence and/or a de novo cost-effectiveness analysis) (Table 2) [29,41,42,48,57,62,66,70−72,74,76]. Examples of prioritization strategies of clinical questions are available as Supplementary Data (Appendix 4.2 Prioritization).

3.4.2. Identification of RUC evidence

Twelve of the 44 organizations (12/44, 27.3%) that explicitly reported considering RUC described the methods to identify relevant RUC evidence. All 12 suggested conducting a review of the available evidence or conducting a review and developing a de novo economic evaluation model, and/or seeking information from GDG members (Table 2) [29,41,42,48,57,61,62,64,66,70−72,74,76,79].

3.4.2.1. Databases, inclusion criteria, and selection of the studies. Six organizations suggested to identify RUC evidence described the databases searched (6/44, 13.6%) (Table 2) [57,62,64,66,70−72,74]. In their approach to identify RUC evidence, a health care system and/or societal perspective were the most common perspectives adopted by the organizations (Table 2) [29,48,57,62,70−72,74,76]. The review of RUC evidence was usually focused on the identification of full economic evaluations [29,57,61,62,70−72,74], but other types of RUC evidence were also considered (e.g., partial economic evaluations or modeling studies) (Table 2). Other eligibility criteria used were internal and external validity of the studies, comparability with a predefined reference case, date of publication or date range (to select most recent studies), country/ies and/or setting, language, and type of study (e.g., economic evaluations based on RCT or SR) [61,66,70−72,74].

Four organizations described a multistep process to select relevant references (4/44, 9.1%) [29,57,62,70−72]. Initially, these organizations assessed the internal validity [70−72], or relevance [57] or applicability [29,62], and depending on the results of this first assessment, they then assessed the external validity [70−72] and methodological quality [29,62,70−72] to identify the references to be considered (Appendix 4.3 Multistep Selection Process). Seven organizations (7/44, 15.9%) reported the use of tools, instruments, or checklists to assess the quality of individual economic studies (Table 2) [29,57,61,62,66,70−72,74].

Table 2. Incorporation of resource use and cost considerations in the clinical practice guidelines

Development process	Frequency (n = 67)	Percentage
RUC considerations included in the CPG		
Yes	59	88.1
No/Not reported	8	12.3
Part of the CPG development process where RUC considerations are included[a]		
Topic selection or topic prioritization process	24	35.8
Scope	13	19.4
Recommendations	55	82.1
Implementation	23	34.3
In other parts of the CPG[b]	2	3.0
RUC included in recommendations		
Yes, explicit	44	65.7
Yes, implicit	5	7.5
Option	6	9.0
No	12	17.9
RUC consideration process[c]		
Prioritization of clinical questions sensitive to RUC	(n = 44)	
Yes	9	20.5
Not reported	35	79.5
Review of RUC evidence		
Methods to identify RUC evidence	(n = 44)	
Yes (SR/de novo economic studies/ information from GDG panel)	12	27.3
Not reported	32	72.7
Person in charge of the economic review		
Health economist and/or systematic reviewer	6	13.6
Not reported	38	86.4
Databases used described		
Yes[d]	6	13.6
Not reported	38	86.4
Terms of search described		
Yes	6	13.6
Not reported	38	86.4
Perspective used		
Health system and/or societal perspective	7	15.9
Health system or others	1	2.3
Not reported	36	81.8
Type of economic studies included		
Full economic evaluations	3	6.8
Full or partial economic evaluations or modeling studies	4	9.1
Not reported	37	84.1
Multistep process to select included studies		
Yes	4	9.1
Not reported	40	90.9
Assessment of the quality of the individual studies—tool/checklist described		
Yes[e]	7	15.9
Not reported	36	81.8
Summarizing and presenting the results of the review		
Yes	5	11.4
Not reported	39	88.6
Development of de novo economic evaluations	(n = 44)	
de novo economic evaluations/ modeling developed		
Yes	8	18.2
Modeling	1	2.3
Unclear	1	2.3
Not reported	34	77.3
Methods to develop de novo economic evaluations/modeling		
Yes, clearly described	4	9.1
Yes, some methods described	3	6.8
Not reported	37	84.1
Summarizing, assessing and presenting findings		
Levels of evidence and strength of recommendation	(n = 67)	
GRADE	25	37.3
GRADE modified	6	9.0
NHMRC	2	3.0
SIGN	2	3.0
Oxford center for evidence-based medicine – levels of evidence	1	1.5
Own system	13	19.4
Other tools (including a mix of different tools)	17	25.4
No formal tool	1	1.5
Moving from evidence to recommendations[c]	(n = 44)	
Assessment of the impact of RUC on recommendations[a]	23	52.3
Qualitative judgment	17	38.6
Cost-effectiveness criterion	9	20.5
GRADE Evidence to Decision frameworks (including RUC considerations)	8	18.2
Not reported	21	47.7

(*Continued*)

Table 2. Continued

Development process	Frequency (n = 67)	Percentage
Economic impact of the recommendations[c]	(n = 44)	
Economic impact of the recommendation described		
Yes, explicit	16	36.4
Yes, implicit	3	6.8
No/not reported	25	56.8
Assessment of the economic impact of the recommendations	19	43.2
Feasibility (usually considered in the recommendation)	5	11.4
Implementation (usually not considered in the recommendation)	11	25.0
Unclear	3	6.8

Abbreviations: RUC, resource use and cost; CPG, clinical practice guideline; GDG, guideline development group; SR, systematic review; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a] One organization could be included in more than one category.

[b] Other: prioritization of the questions to include in the CPG [7–9] or to prioritize CPG for updating [40].

[c] Only organizations that explicitly include RUC when making clinical recommendations.

[d] Most of the institutions use MEDLINE [57,64,66,70–72,74], Embase [64,70–72,74], the Cochrane Library [64,66,74], Health Economic Evaluation Database [57,62,70–72,74], EconLit [70–72,74], or PsycINFO [64,70–72].

[e] The more frequently mentioned are the Quality of Health Economic Studies (QHES) instrument [80], British Medical Journal guidelines for economic submissions established by Drummond and Jefferson on behalf of the BMJ Economic Evaluation Working Party [81], the Consensus on Health Economic Criteria (CHEC) list [82], the Good Practice Guidelines for Decision-Analytic Modeling [83], and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [84].

3.4.2.2. Summarizing and presenting the results of the review. Five organizations provided information about how to summarize and present RUC evidence (5/44, 11.4%) [29,57,61,62,74]. These organizations use tabulated formats (i.e., economic evidence tables) or narrative synthesis (Appendix 4.4 Summary of Results).

3.4.2.3. Development of de novo economic evaluations. Eight organizations reported considering the development of de novo economic evaluations (8/44, 18.2%) [48,57,62,66,70–72,74,76,79] and one reported considering the use of modeling techniques (1/44, 2.3%) (Table 2) [41,42]. Four organizations explicitly described the methods used on how to develop de novo economic evaluations/modeling (4/44, 9.1%) [57,62,70–72,74]. These methods were generally described in form of a reference case that included information about the options compared, the perspective used, the type of study (preferred analytical technique), the health effects included (measure and source of data), the costs included (type of cost and sources of data), the time horizon used, the discount rates applied, and the methods used to explore uncertainty (sensitivity analysis) (Appendix 4.5 de novo EE–Reference Cases). Some organizations suggested performing other types of economic analysis (i.e., cost-consequence analysis) when full economic evaluations were not possible [58,61,62]. None, however, provided guidance on how to conduct such analyses.

3.5. Summarizing, assessing, and presenting findings

Four organizations provided specific guidance on how to summarize economic evidence, assess confidence, and present results for economic evidence (4/44, 9.1%) [29,57,61,62]. All four assessed the following factors to assess the quality of the economic evidence: limitations of design and execution, applicability (or relevance), uncertainty (based on the results of the sensitivity analysis and cost-effectiveness curves), and inconsistency of the results. Two of the four also recommended using specific economic evidence tables, an adaptation of the evidence profile tables developed by GRADE [57,62] (Appendix 4.6 Evidence Profile Table).

3.6. Moving from evidence to recommendations

Twenty-three of the 44 organizations (23/44, 52.3%) that explicitly reported that they considered RUC when formulating recommendations, provided some information about how to consider RUC when formulating recommendations (Table 2) [11,12,15,18,26,30,32,33,37,38,48,55,57,62,64,66,68–72,74–76,78,79,85]. Most organizations suggested making judgments on the balance between the net benefits and the associated RUC (17/44, 38.6%) [11,12,15,32,33,37,38,48,55,57,64,68,69,74–76,78,79,85]. Nine organizations (9/44, 20.5%) explicitly mentioned cost-effectiveness (including incremental cost-effectiveness) as a factor to consider [18,26,30,48,57,62,66,70–72,76], and three (3/44, 6.8%) explicitly suggested a cost-effectiveness threshold [57,62,70–72] (Appendix 4.5 de novo EE–Reference Cases). Finally, eight organizations (8/44, 18.2%) mentioned the use of GRADE Evidence to Decision (EtD) frameworks (Appendix 4.7 Evidence to Recommendation).

3.7. Economic impact of the recommendations

Nineteen of the 44 organizations (19/44, 43.2%) that reported explicitly including RUC evidence in the recommendations suggested assessing the economic impact of the recommendations. Five organizations (5/44, 11.4%) reported explicitly including the economic impact as an aspect to consider when evaluating the feasibility of an intervention (moving from evidence to recommendations stage) [48,57,70–72,76,79]. Eleven organizations included the economic impact of the recommendation in the

implementation section of the CPG (11/44, 25.0%) [30,34,43,44,51,58,62,64,66,74,85] (Appendix 4.8 RUC Implementation).

Seven organizations (7/67, 10.4%) provided guidance in 80% of the five main stages of incorporation of RUC in CPGs (prioritization, SR of evidence, assessment of the quality of the evidence, EtD process, and implementation) [48,57,62,66,70−72,74,76]. Two institutions (2/67, 2.9%) provided guidance in all five [57,62] (Appendix 4.9 RUC Matrix).

4. Discussion

We identified and systematically reviewed the developing guidance documents of 67 international organizations. Our study shows that although most organizations report considering RUC to some extent when developing CPGs, guidance to identify, select, summarize, analyze, and use this information is generally limited and poorly described.

A previous analysis of CPG development methods showed that 57% (17/30) of medical societies in the US explicitly considered cost in their recommendations [2]. In our results, with a higher number of organizations (55/67, 82.1%), considering RUC when developing recommendations could be due to the important differences in the health care models of the organizations included in our sample. Of note for the 12 organizations that provided detailed guidance, only one (1/44, 2.27%) was from the US. Recently, a stepwise 5-step approach on how to conduct a review of the economic evidence in a CPG context was published as a series of articles [89−91]. Guideline organizations could use this and the results of our review alongside high quality manuals identified [57,62], as material to improve the methods reported in their guidance documents.

Although relevant rigorous economic analyses are often available, these are infrequently incorporated in the development of CPGs [92,93]. One reason could be the low transferability of results of the economic studies identified. Economic studies can differ in relation to the population included in the CPG, use a different perspective (which could have an impact on the costs included), or not include all the relevant options of interest [94]. The decision chart developed by Welte et al. to assess and improve transferability of economic evaluations between countries is potentially useful for this purpose. However, this tool probably needs to be adapted to the needs of CPGs developers [95].

In our review, only nine organizations (9/44, 20.5%) report considering the development of de novo economic evaluations or models and all were public or nonprofit organizations. Such evaluations are probably seen as too resource intensive for by many CPG developers, most of whom are small- to medium-size organizations. This possibility highlights the potential important role of using or developing SRs of economic evidence as the main source of RUC evidence.

The assessment of the quality of the economic evidence [94,96] and the presentation of the results in a user-friendly format are also important [96,97]. Our work shows that little attention is paid to this, and that a more structured approach is needed for the guideline context. This should probably mirror the approach used for effectiveness evidence, considering the specific characteristics of economic evidence [93,94,98].

Another relevant aspect is how the economic evidence identified informs GDG decisions, and how does interplays with the rest of factors that decision-makers consider when developing recommendations. Organizations need to be explicit not only about scientific value judgments, such as assessing the quality of the evidence identified, but also social value judgments; for example, judgments about the impact in equity or the balance of equity and efficiency [99]. In our review, only half of the organizations (23/44, 52.3%) that reported considering RUC when developing recommendations describe how they assess the impact of RUC on recommendations. Most of them do qualitative judgments (17/44, 38.6%), and only three (3/44, 6.8%) provide cost-effectiveness thresholds. Although there is controversy around this point, to optimally allocate resources, organizations need to be explicit about what they consider as acceptable trade-offs between costs and effectiveness [94,100]. Organizations can also not consider any economic aspect at all, but again how those decisions are made need to be explicitly described and registered. Recent initiatives such as the use of GRADE EtD frameworks provide a systematic and explicit approach that includes the magnitude of resource use, certainty of evidence of this resource evidence, and cost-effectiveness as part of the set of criteria that are considered when developing recommendations [101]. Eight organizations (8/44, 18.2%) report they are using this framework already, suggesting that there is a gradual uptake by guideline developers.

Our study has some limitations. First, we may not have identified all the handbooks available (e.g., those not indexed or published in the main guideline databases). However, it is unlikely that unidentified handbooks are of higher quality than those that we retrieved, and thus our conclusions are likely to be strengthened. Another limitation is that the evaluation of the handbooks does not necessarily reflect how guidelines organizations implement this guidance in their guidelines. The picture, again, is unlikely to be more optimistic than what we observed.

Considering RUC in CPGs is complex and CPGs developers, especially in organizations that do not have this expertise, may struggle. More and better guidance is urgently needed, and it needs to be implemented across most organizations. This guidance should probably be highly pragmatic given the resource constraints most organizations face.

CRediT authorship contribution statement

Andrea Juliana Sanabria: Conceptualization, Resources, Investigation, Methodology, Formal analysis, Data

curation, Writing - original draft, Writing - review & editing, Project administration. **Anna Kotzeva:** Investigation, Validation, Formal analysis, Writing - original draft, Writing - review & editing. **Anna Selva Olid:** Conceptualization, Resources, Investigation, Writing - review & editing, Methodology. **Sandra Pequeño:** Investigation, Resources, Writing - review & editing. **Robin W.M. Vernooij:** Investigation, Writing - review & editing. **Laura Martínez García:** Investigation, Formal analysis, Writing - review & editing. **Yuan Zhang:** Investigation, Writing - review & editing. **Ivan Solà:** Investigation, Writing - review & editing. **Judith Thornton:** Conceptualization, Methodology, Writing - review & editing. **Pablo Alonso-Coello:** Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Supervision, Writing - review & editing.

Acknowledgments

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.08.004.

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