Methods Future Research Needs Report

Number 2

Frameworks for Determining Research Gaps During Systematic Reviews

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Prepared for:
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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Development of a Framework for Determining Research Gaps During Systematic Reviews

Structured Abstract

Research Objective. Systematic reviews, in addition to summarizing the evidence, generally also discuss needs for future research. However, in contrast to the methods of the systematic review, future needs are not identified systematically. There is limited literature describing organizing principles or frameworks for determining research gaps. We developed and pilot-tested a framework for the identification of research gaps from systematic reviews.

Study Design. We reviewed the research gaps identification practices of organizations involved with evidence synthesis. We contacted: (i) evidence-based practice centers (EPCs) (n=12) associated with the Agency for Healthcare Research and Quality (AHRQ) in the US and Canada, and (ii) other organizations around the world (n=64) that conduct systematic reviews, cost-effectiveness analyses, or technology assessments. Based on the responses, we developed a framework for identifying research gaps. We obtained feedback from two technical experts at our institution and pilot-tested this framework on two randomly selected EPC evidence reports. We also developed a simple, user-friendly worksheet with instructions to facilitate the use of the framework by investigators during or after a systematic review.

Population Studied. Not Applicable.

Principal Findings. Four (33.3%) EPCs and 3 (8.1%) of the other organizations reported currently using an explicit framework to determine research gaps. We did not identify one framework that captured all elements needed to determine and characterize research gaps. Variations of the PICO (population, intervention, comparison, outcomes) framework were most common. It is also important to classify the reason(s) for the gap to help determine how to address the gap. Therefore, we propose a framework that includes both the characterization of the gap using PICOS elements (also including setting) and the identification of the reason(s) why the gap exists. The framework allows investigators to classify reasons for the existence of a research gap as: (a) insufficient or imprecise information, (b) biased information; (c) inconsistency or unknown consistency, and (d) not the right information. We mapped each of these reasons to concepts from three commonly used evidence grading systems: the Grading of Recommendations Assessment, Development and Evaluation (GRADE); the United States Preventive Services Task Force (USPSTF); and the Strength of Evidence (SOE) used by EPCs. This allows leveraging of work already being completed during evidence grading. During pilot-testing, we identified challenges including difficulty in applying the framework for completed systematic reviews and differences in the specificity of research gaps abstracted by different users. These could be tackled with *a priori* discussions amongst investigators. Further testing should determine if these challenges are ameliorated if the framework is used during a systematic review.

Conclusions. We developed a framework to identify and characterize research gaps from systematic reviews. The framework provides for the classification of where and why the current evidence falls short.

Implications for Policy, Delivery, or Practice. In synthesizing evidence, systematic reviews inform health-care decisions for patients, policymakers, and clinicians. Systematic reviews can also be invaluable for identifying research gaps, thus helping develop research agendas. This potential impact of systematic reviews has not been realized. Our framework provides for systematically identifying and characterizing research gaps from systematic reviews. This explicit identification of research gaps will help determine the type of research needed to address the goals of comparative effectiveness research.

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Executive Summary

Background

Evidence reports produced by evidence-based practice centers (EPCs) have always included a future research section. However, in contrast to the explicit and transparent steps taken in the completion of a systematic review, there has not been a systematic process for the development of the future research sections.

Objective

Our objective was to identify and pilot test a framework for the identification of research gaps.

Methods

We used multiple resources and perspectives to help us develop a framework for the identification of research gaps. We carried out the following six steps:

- Step 1: Focused literature review
- Step 2: Review of current practices of evidence-based practices (EPCs)
- Step 3: Review of current practices of organizations involved with evidence synthesis
- Step 4: Development of framework
- Step 5: Pilot test of framework
- Step 6: Refinement and finalization of framework.

Results

Step 1: Focused Literature Review

Our search identified 864 unique citations. After screening, we included five articles published between 2001 and 2009. These addressed a variety of clinical conditions. The organizing principles used in these articles to identify research gaps included key questions, a care pathway, types of participants, interventions, and outcome measures, topic area, and a decision tree.

Step 2: Review of Current Practices of Evidence-Based Practice Centers (EPCs)

Audit of Evidence Reports From EPCs

After stratifying by EPC, we selected 12 evidence reports (from 12 EPCs) randomly. These included 11 clinical reports and one health care services report. Our audit found only two reports that used an explicit framework/set of organizing principles for the identification of research gaps/needs. These involved the description of the gap using the population, intervention, comparison, and outcomes (PICO) framework.

Verification of Abstracted Information

We contacted the 12 EPCs that produced the evidence reports and sought any corrections and clarifications on what we had abstracted from those reports. We obtained feedback from each of these EPCs. Among the EPCs that had not used an explicit framework/set of organizing principles for the identification of research gaps/needs in the evidence reports that we audited, two reported that they had subsequently adopted the PICO framework to identify research gaps.

Step 3: Review of Current Practices of Organizations Involved with Evidence Synthesis

We contacted sixty-four organizations from around the world and obtained responses from 37 (57.8%) organizations. We determined that only four (10.8%) organizations had a formal process for the identification of primary research gaps/needs. Among these organizations, two reported the use of the PICO framework, one reported the use of key questions from guidelines as the organizing principle, and one organization did not specify a framework/organizing principle for organizing research gaps.

Step 4: Development of Framework

Based on the gathered information and for the purpose of systematically identifying and organizing research gaps, we developed a framework that includes (i) the identification of the reason(s) why the research gap exists and (ii) the characterization of the research gap using the PICOS (population, intervention, comparison, outcomes, and setting) elements. The proposed classifications for the reasons for gaps are listed below:

Insufficient or Imprecise Information

Insufficient information can arise if no studies are identified, if a limited number of studies are identified, or if the sample sizes in the available studies are too small to allow conclusions. An imprecise estimate has been defined as one for which the confidence interval is wide enough to include both superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that precludes a conclusion.

Biased Information

This includes information based on studies with significant methodological limitations or suboptimal study designs.

Inconsistent or Unknown Consistency Results

Inconsistent information arises when estimates of effect size from different studies do not appear to go in the same direction or if there are large or significant differences in effect sizes. If there is only one available study, even if considered large sample size, the consistency of results is unknown.

Not the Right Information

This could arise because results from studies might not be applicable to the population and/or setting of interest; the optimal or most important outcomes might not be assessed; or the study duration might be too short to adequately assess some important outcomes.

For each research gap, we recommend that investigative teams identify the reason(s) that most preclude conclusions from being made.

To characterize the gaps we propose identifying which element(s) in the PICOS (population [P], intervention [I], comparison [C], outcomes [O], and setting [S]) framework is (are) inadequately addressed in the evidence.

Worksheet

We designed a worksheet to facilitate the use of the proposed framework in the identification and organization of research gaps during evidence reviews sponsored by AHRQ (see Table A). We envision that investigators would fill out this worksheet soon after the data synthesis phase, while in the process of writing the results section of the evidence report.

Step 5: Pilot Test of Framework

We pilot tested our framework on two randomly selected evidence reports not produced by our EPC. Some (13.6%) research gaps could not be characterized using the framework, and needed to be abstracted in free text form.

Challenges to use of Framework

First, the pilot test was challenging predominantly because we were not involved with the conduct of the evidence review or the writing of its results. Second, only one of the two evidence reports that we used to pilot test our framework included a strength of evidence (SOE) table for each question of interest. This meant that we could not leverage work that would already have been done in the completion of the table. Third, the two research team members who carried out the pilot test abstracted a different number of gaps because of differences in the specificity of the research gaps. Fourth, some research gaps could not be abstracted using the framework and needed to be abstracted in free text form. These gaps related to prevalence, incidence, and the effect of certain factors on prevalence and incidence.

Step 6: Refinement and Finalization of Framework

Changes to the framework and the worksheet at this stage only involved minor formatting and clarification of the instructions.

Discussion

We used multiple resources and perspectives including literature review, contact with other EPCs and organizations involved with evidence synthesis, and consultation with experts at our institution to develop a framework for the identification and characterization of research gaps. This framework involves two main components – identifying explicitly why the research gap exists and characterizing the research gap using widely accepted key elements. This framework facilitates the use of a systematic method to identify research gaps.

Strengths

There are several strengths to the framework we have developed. First, it is based on widely accepted key elements (PICOS) of a well-designed research question. Second, the use of these elements will potentially make the process of identification of research gaps more systematic and therefore useful. Third, for each underlying reason for research gap we have provided the

corresponding domain/element in three common evidence grading systems. Fourth, the framework characterizes the research gap, including the reason(s) for the existence of the gap.

The worksheet is simple to use and facilitates the presentation of research gaps. It is transparent and reproducible. The use of a worksheet may be beneficial in two main ways. First, it would facilitate discussion about research gaps between team members who might have written the results for different key questions. Second, the worksheet would enable investigative teams to write the future research section in a more organized and systematic manner.

We did not find consistency in how research gaps were presented during our audit of the evidence reports. We propose that while writing the future research needs sections of evidence reports, investigative teams provide adequate details of research gaps and translate them into research questions. We propose that EPCs use the following format for presenting research gaps in evidence reports.

Key Question Number and Key Question Topic

- Research Gap Number
- Reason for Gap
- Population (P)
- Intervention (I)
- Comparison (C)
- Outcomes (O)
- Setting (S).

Research Question

Limitations and Future Research

We identified limited use of formal processes, including frameworks, for identifying research gaps. This prevented us from addressing whether one method for identifying research gaps is more valid than another or whether one format for presenting research gaps is more useful than another.

A limitation of the framework that we have developed is that it does not explicitly account for the specificity of research gaps. Team members could differ in terms of the number of research gaps abstracted based on whether gaps are abstracted at the level of the key question or the subquestion. We therefore suggest that a priori decisions be made about the level of specificity that should be accomplished and that investigative teams be consistent.

Our framework calls for identifying the most important reason(s) for existence of research gaps (i.e., reasons that most preclude conclusions from being made). However, there may often be more than one main reason why a research gap exists. Team members could differ on the relative importance of these reasons. More research is needed to determine if a hierarchy or a ranking system can be established to aid these decisions.

The application of the framework to retrospectively identify research gaps by our investigative team was quite challenging. We suggest that the same investigative team that synthesizes the evidence apply the framework while writing the results. We also suggest that investigative teams working on evidence reports use the SOE table for grading the evidence. If this is done, teams can leverage work completed in preparing the table to identify research gaps.

Conclusions

We searched the literature, conducted an audit of EPC evidence reports, and sought information from other organizations involved with evidence synthesis. Despite these efforts, we identified little detail or consistency in the frameworks used to determine research gaps within systematic reviews. In general, there is no widespread use or endorsement of a specific formal process or framework for identifying research gaps using systematic reviews.

We developed a framework to facilitate the systematic identification of research gaps through the classification of where the current evidence falls short and why the evidence falls short. A worksheet was developed to facilitate the use of the framework when completing a systematic review and thus facilitate the use of a systematic process to identify research gaps.

Table A. Step 4: Development of framework—Research gaps abstraction worksheet

<Project Name>
Research Gap Worksheet
Page ____ of ____
Key Question Number – _____

Completed by – _____
Date – _____

Serial **N**o.	Reason(s) for **G**ap*	**Population (P)**	**Intervention (I)**	**Comparison (C)**	**Outcomes (O)**	**Setting (S)**	**Free Text of Gap**	**Notes**
Example	**B**	Women with gestational diabetes	Metformin	Any insulin	Neonatal hypoglycemia, NICU admissions	-		-
Example	**D**	-	-	-	-		How should the physician assess asthma or bronchodilator responsiveness?	

* Reasons for Gap:
A. Insufficient or imprecise information
B. Biased information
C. Inconsistency or unknown consistency
D. Not the right information.

Background

During the completion of a systematic review, investigators routinely identify gaps in the available evidence. Evidence reports produced by evidence-based practice centers (EPCs) have always included a future research section. However, in contrast to the explicit and transparent steps taken in the completion of a systematic review, there has not been a systematic process for the development of the future research sections.

With a goal of ultimately developing guidance for the EPC program, AHRQ asked EPCs to respond to seven questions about the development, prioritization, and presentation of research needs (see Appendix A). The JHU EPC was assigned question 1, which is the following question:

Define frameworks for determining research gaps conducted within a systematic review.

a. i. What are the various frameworks (concepts and organizing principles) used to determine the research gaps within a systematic review?
   ii. How often do the identified gaps extend beyond the reach of the original key questions?
b. Is there any evidence that one method for identifying research gaps is more valid than another?
c. Is there any evidence that one format for presenting research gaps is more useful than another?

We defined a research gap as a topic or area for which missing or inadequate information limits the ability of reviewers to reach a conclusion for a given question. A research need was defined as a gap that limits the ability of healthcare decisionmakers (patients, physicians, policy makers, etc.) from making decisions. A research gap may not be a research need if filling the gap would not be of use to stakeholders that make decisions in healthcare. Our project focused on research gaps, but we broadened our methods to include "research needs" since this distinction is not always made. While prioritization of research needs and assessment of feasibility of various study designs may have been considered in processes by other organizations as noted later in the report, these were not within the scope of the above questions.

Objective

Our objective was to identify and pilot test a framework for the identification of research gaps.

Methods

We used multiple resources and sought different perspectives to develop a framework for the identification of research gaps. We carried out six steps. We first attempted to identify, enumerate and describe frameworks that have been used (steps 1 to 3). We then developed, tested and refined a framework (steps 4 to 6). The six steps are:

1. Focused literature review
2. Review of current practices of evidence-based practice centers (EPCs)
3. Review of current practices of organizations involved with evidence synthesis
4. Development of framework
5. Pilot test of framework
6. Refinement and finalization of framework.

Step 1: Focused Literature Review

We sought English-language articles that described the identification of research gaps, research needs, or evidence gaps from systematic reviews or related processes such as health technology assessments (HTAs). We completed a search of MEDLINE© via PubMed (April 22, 2010). We analyzed the terms used in eligible articles identified during preliminary searching to develop a search strategy. We combined controlled vocabulary terms and text words for systematic review, meta-analysis, evidence-based medicine, research needs, and research gaps to create the following search strategy:

> ((review literature as topic[mh] OR meta-analysis as topic[mh] OR evidence-based medicine[mh] OR systematic reviews[tiab] OR systematic review[tiab] OR technology assessment[tiab] OR technology assessments[tiab] OR meta-analysis[tiab] OR meta-analyses[tiab]) AND (research needs[tiab] OR gaps[tiab] OR research priorities[tiab])).

All search results were imported into a database maintained in reference management software (ProCite™, Thomson Reuters, New York, NY). A custom workform was used to track the searching and screening processes. All citations were screened for eligibility at the title and abstract level by one reviewer. Citations deemed eligible or of unclear eligibility were reviewed by a second reviewer. We obtained full-text articles of citations confirmed as eligible or of unclear eligibility. These full-text articles were then independently screened by two reviewers. Disagreements concerning eligibility were resolved by consensus or by a third reviewer. We excluded citations from further consideration if they:

- Were not in English;
- Did not have an objective to identify research gaps/needs;
- Did not use a systematic review or similar process to identify research gaps/needs;
- Did not include a description of methods or process for identifying research gaps/needs; or
- Were otherwise eligible but used guidelines as basis for identification of research gaps/needs.

We scanned the reference lists of included articles. From each included article we abstracted the topic area and the method of identifying research gaps/needs that was described in the text or

figures. We also abstracted the organizing principle(s) that was (were) used to identify research gaps/needs.

Step 2: Review of Current Practices of Evidence-based Practice Centers (EPCs)

Audit of Evidence Reports From EPCs

We searched the AHRQ website (http://www.ahrq.gov/) for evidence reports that satisfied the following criteria (as of April 12, 2010):

- Published in 2008 or later;
- Classified as "Clinical" or "Health Care Services" (we did not consider "Technical" reports); and
- Produced by an EPC that is part of AHRQ's EPC program between 2007 and 2012.

We randomly selected one report if there was more than one report that satisfied the above criteria from the same EPC. One team member abstracted the following data from each of the evidence reports using a form designed in Excel (Microsoft™, Redmond, WA) (see Appendix B for data abstraction form):

- Whether or not the terms research gaps/needs were defined;
- Whether or not there was a description of how research gaps/needs were identified;
- Whether or not there was an explicit framework/set of organizing principles used for the identification of research gaps/needs;
- Whether or not research gaps/needs were presented;
- Location(s) of presentation of research gaps/needs in the report; and
- How research gaps/needs were presented (e.g., an unordered list, separated by key question, separated by type of study, as a figure/conceptual framework).

Verification of Abstracted Information

We contacted the EPCs that produced the evidence reports selected for abstraction. We contacted the primary author of the evidence report. If it was unclear who the primary author was, or if we were not able to contact the primary author, we contacted the current director of the EPC that produced the report. We provided a summary of what was abstracted from the report and asked for any corrections and clarifications. If no explicit framework was identified in our review of the report, we asked if the EPC had implemented a process since the publication of the report. If so, the EPC was asked to provide a description of the process and to indicate when it was implemented. Each EPC was contacted via email.

Step 3: Review of Current Practices of Organizations Involved With Evidence Synthesis

We identified organizations that develop systematic reviews or related products such as HTAs. We compiled a list by pooling together organizations from the following two sources:

- All current member organizations of the International Network of Agencies for Health Technology Assessment (INAHTA) (as listed on the INAHTA website http://www.inahta.org/ on April 27, 2010); and
- All current member organizations of the Guidelines International Network (G-I-N) from the United States (US), United Kingdom (UK), Canada, and Australia that are involved with systematic reviews, technology assessments (TA), or cost-effectiveness analyses (CEA) (as listed on the G-I-N website http://www.g-i-n.net/ on April 27, 2010).

Each organization was contacted via email and asked:

- Whether or not they have a formal process for identifying research gaps/needs;
- When the formal process (if any) for identifying research gaps/needs was implemented; and
- To provide a description of the formal process (if any).

Based on responses received from these organizations, we made independent determinations of whether the processes were formal or not. We determined processes to be formal if the organization stated that it had a formal process currently being implemented and if the process or method used was explicitly described. If formal, we assessed whether the process was directed at the identification of gaps/needs for primary research, systematic reviews, HTAs, and/or guidelines. We only included for further consideration the formal processes used by organizations for the identification of research gaps/needs for primary research.

Step 4: Development of Framework

We considered the various elements of research gaps noted in the literature and identified by the EPCs and organizations. Based on these elements and known important aspects of research questions, we developed a framework for the identification and organization of research gaps. This framework included an explicit determination and classification of the reason(s) why each research gap exists. We developed a worksheet to facilitate the use of the framework by investigators to systematically identify, organize, and record research gaps identified during the conduct of an evidence report.

Technical Expert Review

Once we developed the initial version of the framework, we sought feedback from two technical experts from our institution. We asked these experts to review the framework and the worksheet and to comment on the clarity and potential ease of use. We also asked them to provide general comments and suggestions for specific items that might need to be added, removed, or reworded. The framework and worksheet were refined after receipt of feedback from the technical experts.

Step 5: Pilot Test of Framework

Selection of EPC Evidence Reports for Pilot Test

We pilot tested the framework on two evidence reports not produced by our EPC. These reports were randomly selected from a pool of available reports from the AHRQ Web site (http://www.ahrq.gov/) which met the following criteria (as of August 02, 2010): published in 2008 or later; classified as "Clinical" or "Health Care Services" (we did not consider "Technical" reports); and produced by an EPC that is part of AHRQ's EPC program between 2007 and 2012.

Process for Pilot Test of Framework

Two team members independently applied the framework to each selected evidence report using the worksheet. The purpose was to assess the usability of the worksheet in abstracting and identifying research gaps. We decided to focus on the results sections because we wanted to simulate, as closely as possible, the process that investigators would follow in using this framework and worksheet. We envision that investigators would fill out this worksheet soon after the data synthesis phase, while writing the results section of the evidence report. Team members thus read the results sections of the reports to abstract individual research gaps. If necessary, team members read other sections of the reports. Team members also kept track of the number of key questions, number of research gaps abstracted, and number of gaps which were abstracted but could not be fit into the framework. We recorded the time taken to complete this process per evidence report. After reviewing the evidence reports and abstracting research gaps, we compared the lists of gaps identified by the two team members. We also compared the gaps we identified with those presented in the future research sections of the respective evidence reports.

Step 6: Refinement and Finalization of Framework

We refined the framework and the worksheet based on our results from the pilot test.

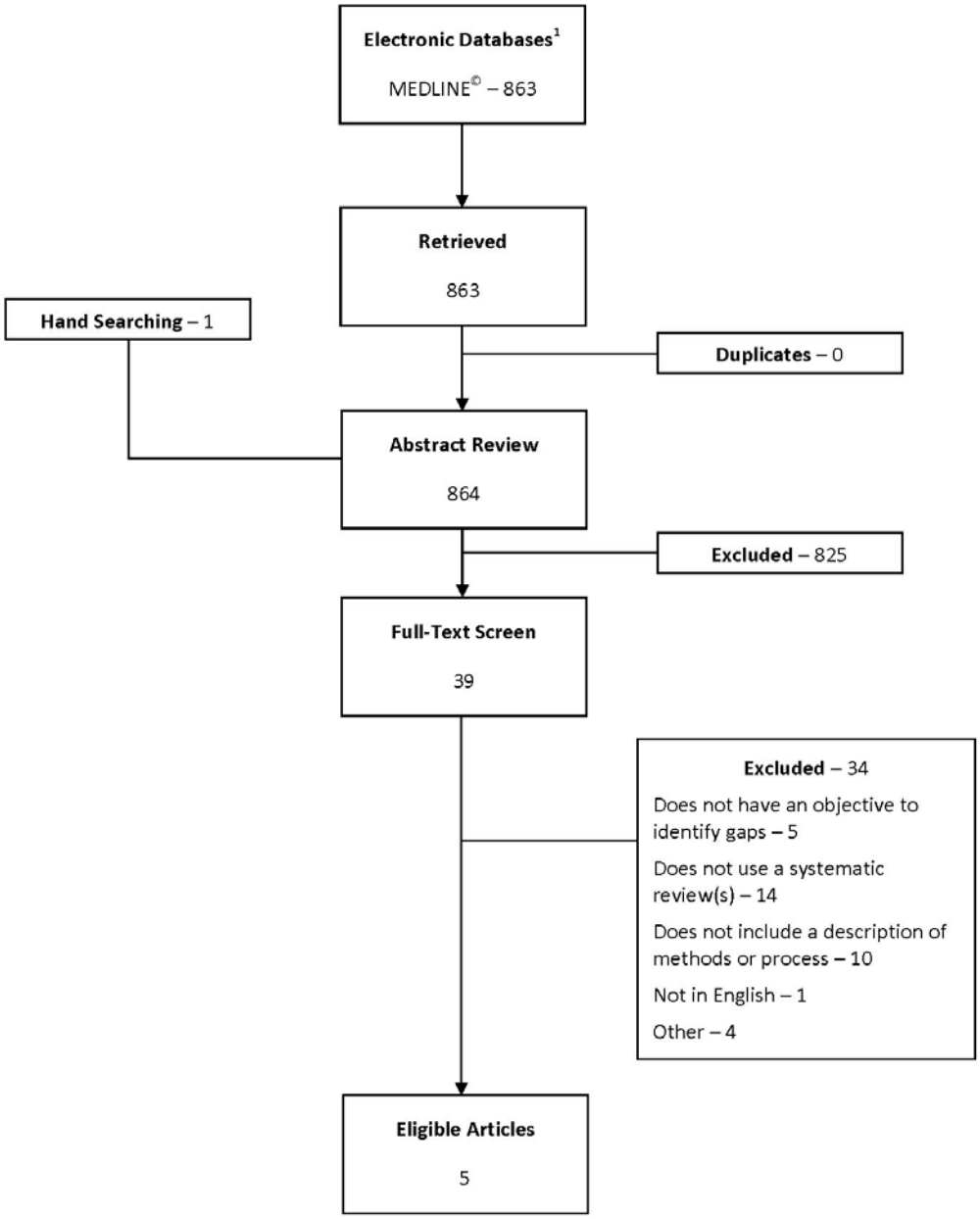
Results

Step 1: Focused Literature Review

Our search identified 864 unique citations. Eight hundred and twenty-five (95.5%) of these were excluded from further consideration during title and abstract screening. The primary reasons for exclusion at this level were: did not have an objective to identify gaps/needs (n=619), did not use a systematic review (n=119), and did not include a description of methods/process (n=12). Of the 39 articles screened at full-text, 34 (87.2%) were excluded. The primary reasons for exclusion of full-text articles were: article did not use a systematic review (n=14), article did not include a description of methods/process for identifying research gaps/needs (n=10), and article did not have an objective to identify gaps/needs (n=5). We thus included five articles in the focused literature review.[1-5] Figure 1 provides a summary of the searching and screening process.

Table 1 describes the five included articles,[1-5] published between 2001 and 2009. These addressed a variety of conditions—chronic noncancer pain,[1] sexually transmitted infections (STIs) in teenagers,[2] acute pain management in children and young people,[2] infertility,[4] and chronic benign pain syndromes.[5] One article was not specific to any particular clinical topic area.[3]

Figure 1. Step 1: Focused literature review—Summary of search and review process



[1]MEDLINE© was accessed via PubMed.

Table 1. Step 1: Focused literature review—Summary of included articles with methods/frameworks used

Author (Year)[Ref]	Topic Area	Relevant Text From Article	Summary of Method/Framework Used
Chou (2009)[1]	Chronic non-cancer pain	To assign an overall strength of evidence (good, fair, or poor), the number, quality, and size of the studies; consistency of results between studies; and directness of the evidence were considered. ● Consistent results from a number of higher-quality studies across a broad range of populations support a high degree of certainty that the results of the studies are true (the entire body of evidence would be considered ''good-quality''). ● For a ''fair-quality'' body of evidence, results could be due to true effects or due to biases present across some or all of the studies. ● For a ''poor-quality'' body of evidence, any conclusion is uncertain due to serious methodological shortcomings, sparse data, or inconsistent results.	Research gaps were identified as the key questions that were addressed by only "poor-quality" evidence. Organizing Principle(s) - Key question.
Shepherd (2007)[2]	● STIs in teenagers ● Acute pain manage-ment in children and young people (28 days - 19 years)	The included literature was read, assimilated, and mapped to the appropriate nodes of the care pathway. This process was performed by one researcher and checked by a second. Additional areas for intervention along the care pathway were identified during this assimilation process. Validation of this process was undertaken by an independent reviewer. The quality of the guidelines was appraised narratively using the AGREE appraisal tool. Analysis of the populated care pathway and narrative map (the framework based on the care pathway) facilitated the identification of gaps in research evidence and policy literature. The gaps were identified by (i) analyzing those areas of the care pathway lacking appropriate guidelines/guidance or evaluation research, (ii) noting gaps cited within existing guidelines/guidance or evaluation research, and (iii) identifying poor-quality and out-of-date studies and guidelines/guidance.	A care pathway was developed for each condition. Gaps were identified using the following three criteria to assess areas within the care pathway: ● analyzing those areas of the care pathway lacking appropriate guidelines/guidance or evaluation research, ● noting gaps cited within existing guidelines/guidance or evaluation research, and ● identifying poor-quality and out-of-date studies and guidelines/guidance. Organizing principle(s) - Care pathway.
Clarke (2007)[3]	Not specific	One author read each record and categorized it on the basis of whether a recommendation was made as to the need for more research and, if so, whether suggestions were made regarding the specific types of intervention, participant, or outcome measures that should be assessed or included in future research. In addition, suggestions for a new, expanded, or updated systematic review were noted. Another author read each record to identify whether it mentioned a specific ongoing or planned study. The third author read each record, checked the assigned codes, and made the final decision on the coding of each record. Subsequently, details were obtained on the content of the "ongoing studies" sections. The number of studies listed for each review was counted and cross-checked by two of the authors.	Uses the Implications for Research sections of all Cochrane reviews from one issue of the Cochrane Library (various topics). Reviews were categorized by whether a recommendation was made as to the need for more research and, if so, whether suggestions were made regarding the types of intervention, participant, or outcome measures that should be included in future research. In addition, suggestions for a new, expanded, or updated systematic review were noted. It was also noted whether reviews mentioned a specific ongoing or planned study. Subsequently, details were obtained on the content of the "ongoing studies" sections. Organizing principle(s) - By types of intervention, types of participant, and types of outcome measures.

Table 1. Step 1: Focused literature review—Summary of included articles with methods/frameworks used (continued)

Author (Year)[Ref]	Topic Area	Relevant Text From Article	Summary of Method/Framework Used
Johnson (2003)[4]	Infertility	The following information as collected from each review: the number of trials available for meta-analysis, the total number of trial participants available for meta-analysis and whether there was an answer to the primary clinical question-into which category from (A) to (C), below, the review fell: (A) Where there is evidence of effectiveness or harm from a metaanalysis of trial data. The term "relative effectiveness" was used when two interventions were compared and the term "effectiveness" was used when the treatment was compared with either placebo or no treatment. (B) Where there is insufficient evidence of effectiveness and the review authors have called for further research. (C) Where there is insufficient evidence of effectiveness and the review authors have not called for further research.	Uses Cochrane reviews to identify areas of insufficient evidence. Gaps were identified if one of the following two criteria were fulfilled (based on review authors' definition of the sufficiency of evidence): ● Where there is insufficient evidence of effectiveness and the review authors have called for further research. ● Where there is insufficient evidence of effectiveness and the review authors have not called for further research. Organizing principle(s) - Topic area.
de Vet (2001)[5]	Chronic benign pain syndromes	The methodologic quality of the relevant reviews was assessed according to the method developed by Assendelft et al. on a 0–100 point scale. If reviews of reasonable (60–79 points) to good quality (≥80 points) were found, their conclusions (effective, not effective, inconclusive) were adopted. If only reviews of poor or moderate quality were found, a new systematic review was recommended. If no recent reviews of a specific topic were found, a search was made for randomized controlled trials (RCTs), using the strategy recommended by the Cochrane Collaboration. If there were more than five RCTs in the computerized databases mentioned above, a systematic review was recommended. If there were five RCTs or less, the following data were extracted from the abstract: the design (parallel or a crossover study), the sample size, whether the trial was really randomized, whether it was blinded, which interventions were compared, and the conclusions. If the conclusions were inconsistent, a new RCT was recommended. If the results appeared to be consistent, it was advised that the evidence of (in)effectiveness should be studied in detail in order to decide on the level of evidence. When the evidence from a small number of studies is convincing, it should be incorporated in a clinical guideline. A decision tree was used for this purpose for each intervention-syndrome combination (topic). This resulted in a list of topics for the nine chronic benign pain syndromes for which systematic reviews were recommended and a list of topics for which new RCTs were needed.	A decision tree was generated to decide about the need for a new systematic review or the need for a new RCT for each topic. Lists of research gaps/needs were identified as areas of insufficient or inconsistent evidence. These lists were then prioritized. Organizing principle(s) - Decision tree

Abbreviations: AGREE=appraisal of guidelines research and evaluation, RCT=randomized controlled trial, STI=sexually transmitted infection.

Chou et al. (2009) organized research gaps by key question.[1] Research gaps were identified as key questions for which there was "poor quality" body of evidence. The authors defined evidence to be of poor quality if any conclusion was uncertain due to serious methodological shortcomings, sparse data, or inconsistent results.[1]

Clarke et al. (2007) used the "Implications for Research" sections of all Cochrane reviews from a single issue (Issue 4, 2005) of The Cochrane Library to identify research gaps.[3] Research gaps were identified based on whether a recommendation was made as to the need for more research, and if so, whether review authors made suggestions regarding the specific types of intervention, participant, or outcome measures that should be assessed or included in that research.[3] Johnson et al. (2003) also used Cochrane reviews to identify research gaps/needs.[4] They organized research gaps/needs by topic area and identified research gaps/needs as topics where there was insufficient (as defined by the review authors) evidence, whether or not review authors called for further research.[4]

Shepherd et al. (2007) developed care pathways for the management of STIs in teenagers and for the acute pain management in children and young people (28 days to 19 years of age).[2] Research gaps/needs were identified within the care pathway as areas lacking appropriate guidelines/guidance or evaluation research; areas with gaps cited within existing guidelines/guidance or evaluation research; or areas with poor-quality and out of date studies and guidelines/guidance.[2] De Vet et al. (2001) generated a detailed decision tree to decide about the need for a new systematic review or the need for a new randomized controlled trial (RCT) for each topic.[5] Research gaps/needs were identified as areas of insufficient or inconsistent evidence. Two lists of research gaps/needs were generated (one for systematic reviews and one for RCTs) and then prioritized.[5]

Table 1 also provides a summary of the method/framework used by the authors of the articles for the identification of research gaps/needs. The organizing principles included key question;[1] a care pathway;[2] types of participants, interventions, and outcome measures;[3] topic area;[4] and a decision tree.[5] The literature described in varying detail how research gaps were defined or identified. Specifics on what was described are also provided in Table 1.

Step 2: Review of Current Practices of Evidence-based Practice Centers (EPCs)

Audit of Evidence Reports From EPCs

As of April 20, 2010 there were fourteen current EPCs (as listed on the AHRQ website). These EPCs had produced a total of twenty-nine eligible evidence reports (mean 2.4 per EPC, median 1.5 per EPC, range 0 to 7). These included twenty-six clinical reports and three health care services reports. Two EPCs (ECRI EPC and University of Connecticut EPC) had not produced any evidence report after 2008 that met our inclusion criteria.

The twelve evidence reports randomly selected after stratification by EPC (one from each remaining EPC) are listed in Table 2.[6-17] These included eleven clinical reports[6-9,11-17] and one health care services report.[10] The topic areas covered included: obstetric and gynecological conditions (three reports);[7,11,12] cancer and blood disorders (two reports);[6,8] complementary and alternative care (one report);[9] information technology (one report);[10] dietary supplements (one report);[13] metabolic, nutritional, and endocrine conditions (one report);[14] mental health conditions and substance abuse (one report);[15] heart and vascular diseases (one report);[16] and kidney/urological conditions (one report).[17]

Table 2. Step 2: Review of current practices of evidence-based practice centers (EPCs)—Summary of randomly selected evidence reports

Sr no.	EPC Name	Type of Report	Topic Area	Title of Evidence Report, Ref	Year of Release
1	Blue Cross and Blue Shield Association	Clinical	Cancer & blood disorders	HER2 testing to manage patients with breast cancer or other solid tumors[6]	2008
2	Duke University EPC	Clinical	Obstetric and gynecologic conditions	Effectiveness of assisted reproductive technology[7]	2008
3	Johns Hopkins University EPC	Clinical	Cancer & blood disorders	Impact of gene expression profiling tests on breast cancer outcomes[8]	2008
4	McMaster University EPC	Clinical	Complementary & alternative care	Complementary and alternative medicine in back pain utilization report[9]	2009
5	Oregon EPC	Health Care Services	Information technology	Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved[10]	2008
6	RTI International - UNC EPC	Clinical	Obstetric and gynecologic conditions	Outcomes of maternal weight gain[11]	2008
7	Southern California/ RAND EPC	Clinical	Obstetric and gynecologic conditions	Bariatric surgery in women of reproductive age: Special concerns for pregnancy[12]	2008
8	Tufts University EPC	Clinical	Dietary supplements	Vitamin D and calcium: A systematic review of health outcomes[13]	2009
9	University of Alberta EPC	Clinical	Metabolic, nutritional, and endocrine conditions	Diabetes education for children with type 1 diabetes mellitus and their families[14]	2008
10	University of Minnesota EPC	Clinical	Mental health conditions and substance abuse	Integration of mental health/substance abuse and primary care[15]	2008
11	University of Ottawa EPC	Clinical	Heart and vascular diseases	Diagnosis and treatment of erectile dysfunction[16]	2009
12	Vanderbilt University EPC	Clinical	Kidney/ urological conditions	Treatment of overactive bladder in women[17]	2009

Abbreviations: EPC=evidence-based practice center, HER2=human epidermal growth factor receptor 2, RAND=Research and Development, RTI=Research Triangle Institute, UNC=University of North Carolina

Table 3 presents a summary of our audit of these twelve evidence reports. None of the reports defined what was meant by research gaps or research needs. Only one (8.3%) report used an explicit framework/set of organizing principles for the identification of research gaps/needs.[9] This involved the description of the gap using the population, intervention, comparison, and outcomes (PICO) framework.

Table 3. Step 2: Review of current practices of evidence-based practice centers (EPCs)—Audit of randomly selected evidence reports

Sr No	EPC Name (Ref no.)	Were the Terms "Research Gaps" or "Research Needs" Defined?	Was There a Description of how Research Gaps/ Needs Were Identified?	Was There an Explicit Framework (e.g., PICO) for Identifying Research Gaps/Needs?	Were Future Research Gaps/Needs Provided, and Where Were They Found?	How Were Research Gaps/Needs Presented?
1	Blue Cross and Blue Shield Association[6]	No	No	No	Yes, discussion section	Bullet-point list
2	Duke University EPC[7]	No	No	No	Yes, separate chapter	Bullet-point list
3	Johns Hopkins University EPC[8]	No	No	No	Yes, discussion section	Numbered list
4	McMaster University EPC[9]	No	No	Yes, PICO framework	Yes, discussion section	Numbered list
5	Oregon EPC[10]	No	No	No	Yes, separate chapter	Embedded in text
6	RTI International - UNC EPC[11]	No	No	No	Yes, discussion section	Bullet-point list
7	Southern California/ RAND EPC[12]	No	No	No	Yes, discussion section	Embedded in text
8	Tufts University EPC*[13]	No	Yes	Yes, PICO framework	Yes, separate chapter	Table
9	University of Alberta EPC[14]	No	No	No	Yes, discussion section	Bullet-point list
10	University of Minnesota EPC[15]	No	No	No	Yes, discussion section	Table
11	University of Ottawa EPC[16]	No	No	No	Yes, discussion section	Embedded in text
12	Vanderbilt University EPC[17]	No	No	No	Yes, discussion section	Bullet-point list

Abbreviations: EPC=evidence-based practice center, PICO=population, intervention, comparison, and outcomes=RAND=Research and Development, RTI=Research Triangle Institute, UNC=University of North Carolina

* This EPC's report was initially classified as not having provided research gaps/needs. However, after clarification from the EPC during the verification of the audit, this report was subsequently classified as having provided research gaps/needs in a table in a separate chapter using the PICO framework.

All reports provided future research gaps/needs (see Table 3). Of these, nine (75%)[6,8,9,11,12,14-17] reports provided future research gaps/needs in the discussion section while three (25%)[7,10,13] provided them in a separate chapter. Five (41.7%)[6,7,11,14,17] separated out research gaps/needs using bulleted lists; three (25.0%)[10,12,16] embedded research gaps/needs in text; two (16.7%)[8,9]

separated research gaps/needs using numbered lists; and two (16.7%)[13,15] presented research gaps/needs in tables.

Verification of Abstracted Information

We contacted the twelve EPCs which produced the evidence reports and sought any corrections and clarifications on what we had abstracted from those reports. We obtained feedback from each of these EPCs.

A summary of the responses from the EPCs is available in Appendix C. Although we had initially classified only one report[9] as using an explicit framework (PICO), we reclassified a second report[13] as using the PICO framework after receiving feedback from the EPC. Two additional EPCs reported that they had subsequently adopted the PICO framework to characterize research gaps. Thus, four of twelve (33.3%) EPCs currently use the PICO framework to characterize research gaps.

Several of the EPCs provided further details about how they define or identify research gaps, including areas with no studies identified; studies with methodological issues contributing to low quality; studies with insufficient information on important subgroups or outcomes; etc. Details are provided in Appendix C.

Step 3: Review of Current Practices of Organizations Involved With Evidence Synthesis

Sixty-four organizations met our inclusion criteria and are listed in Appendix D. These included seven each from Australia, the UK, and the US, six from Spain, five from Canada, and thirty-two from other countries. As of April 27, 2010, fifteen organizations were involved with the conduct of systematic reviews, fifty-five with HTAs, and four with CEAs. Seven organizations were involved with the conduct of more than one of these activities.

We obtained responses from thirty-seven organizations (response rate = 57.8%), including seven from Australia, five from Canada, five from the UK, four from the United States, two from Spain, and fourteen from other countries. Among these thirty-seven organizations, fifteen (40.5%) reported having a formal process to identify research gaps/needs (see Table 4). However, we determined that only four of these fifteen organizations had a formal process for the identification of primary research gaps/needs. The other eleven organizations reported processes that did not meet our definition of a formal process (n=9) or were formal processes for the identification of needs for systematic reviews and HTAs (n=1) or guidelines (n=1). We thus determined that four (10.8%) of the thirty-seven organizations had a formal process for the identification of primary research gaps/needs (see Appendix E and Table 4).

Table 4. Step 3: Review of current practices of organizations involved with evidence synthesis—Summary of organizations which reported having formal processes

Sr No	Country	Organization Name	Our Determination of Nature of Reported Process	Organizing Principle
1	Australia	Caring for Australasians with Renal Impairment	Process is not formal	-
2	Australia	Joanna Briggs Institute	Process is not formal	-
3	Canada	Canadian Agency for Drugs and Technologies in Health	Process is not formal	-
4	Canada	Program in Evidence-based Care	Process is formal, identifies gaps/needs for: - Guidelines	None identified
5	Finland	Finnish Office for Health Technology Assessment	Process is not formal	-
6	Italy	HTA Unit in A. Gemelli Teaching Hospital	Process is not formal	-
7	New Zealand	Health Services Assessment Collaboration	Process is formal, identifies gaps/needs for: - Systematic reviews - HTAs	PICO
8	Spain	Catalan Agency for Health Information, Assessment and Quality	Process is formal, identifies gaps/needs for: - Primary research	None identified
9	Sweden	The Swedish Council on Technology Assessment in Health Care	Process is not formal	-
10	The Netherlands	The Medical and Health Research Council of The Netherlands	Process is not formal	-
11	UK	National Institute for Health and Clinical Excellence	Process is formal, identifies gaps/needs for: - Systematic reviews - Primary research	PICO
12	UK	NIHR Coordinating Centre for Health Technology Assessment	Process is not formal	-
13	UK	Scottish Intercollegiate Guidelines Network	Process is formal, identifies gaps/needs for: - Primary research	Key question
14	US	American Academy of Otolaryngology - Head and Neck Surgery Foundation	Process is not formal	-
15	US	National Kidney Foundation	Process is formal, identifies gaps/needs for: - Primary research	PICOD

Abbreviations: HTA=health technology assessment, NIHR=National Institute for Health Research, PICO=population, intervention, comparison, and outcomes, PICOD=population, intervention, comparison, outcomes, and time points, UK=United Kingdom, US=United States

Two organizations reported the use of the PICO framework for identifying research gaps/needs. These included the National Kidney Foundation (NKF) in the US and the National Institute for Health and Clinical Excellence (NICE) in the UK. NKF reported the use of the PICOD framework which, in addition to the elements in the PICO framework, includes the element of time points for outcomes measurement (D).

The Scottish International Guidelines Network (SIGN) used key questions from guidelines as the organizing framework while identifying research gaps/needs. It was reported that if a

question is seen as particularly important and there is no evidence, or only such poor evidence that the guideline development group does not feel able to make a recommendation, then a recommendation for further research is made.

Step 4: Development of Framework

We did not identify one framework that we felt captured all elements needed to determine research gaps. Variations of the PICO framework were used by some EPCs and other agencies to characterize research gaps. We thus include this as part of our proposed framework. However, we felt it was also important to classify the reason(s) for the gap to help to determine how to address the gap. Therefore, based on information from steps 1 through 3, we propose a framework that includes (i) the identification and classification of the reason(s) why the research gap exists and (ii) the characterization of the research gap using the PICOS (population, intervention, comparison, outcomes, and setting) elements.

We propose that the most important reason(s) for the existence of the research gap be chosen. The reason(s) selected should be those that most preclude conclusions from being made. Put another way, investigative teams should consider what would be needed to allow for conclusions to be made. The proposed classification of the reasons for research gaps includes:

- Insufficient or imprecise information
- Biased information
- Inconsistency or unknown consistency
- Not the right information.

We recognize that there is an overlap with identifying gaps and the tasks completed during the grading of the evidence. To facilitate leveraging the work being completed during the grading, we have included with each description the corresponding domain/element in three common evidence grading systems: the EPC Strength of Evidence (SOE)system;[18] the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system;[19] and the United States Preventive Services Task Force (USPSTF) system.[20]

A. Insufficient or Imprecise Information

Insufficient information can arise if no studies are identified, if a limited number of studies are identified, or if the sample sizes in the available studies are too small to allow conclusions about the question of interest. If the information available in identified studies is insufficient to allow a conclusion or if the estimate of the effect (usually achieved from a meta-analysis) is imprecise there is a research gap. Precision is the degree of certainty surrounding the effect estimate.[18] An imprecise estimate has been defined as one for which the confidence interval is wide enough to include both superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that precludes a conclusion.[18] Imprecision in the meta-analytic effect estimate may result as a consequence of a small number of studies in the meta-analysis or small sample sizes in included studies (leading to imprecision in individual study effect sizes). Where meta-analysis is not conducted, imprecision of the individual studies should be evaluated.

Correspondence to grading systems:

- *EPC SOE:* **Precision** is a required domain.
- *GRADE*: The GRADE Working Group advises decreasing the grade of the quality of the evidence if the data are “imprecise or sparse”.
- *USPSTF:* The following questions are considered while grading the evidence:

- "How many studies have been conducted that address the key question(s)?"
- "How large are the studies? (i.e., what is the precision of the evidence?)"

B. Biased Information

Various criteria exist for assessing the risk of bias of studies of different study designs. The aggregate risk of bias is contingent upon the risk of bias of the individual studies.[18] In addition to considering methodological limitations of studies, the appropriateness of the study design should also be considered. An example of a research gap that arises due to methodological limitations of existing studies is: There is a need for more randomized controlled trials with outcome assessor blinding to compare the effects of various newer oral diabetes agents in women with gestational diabetes.

Correspondence to grading systems:

- *EPC SOE:* **Risk of bias** is a required domain. It incorporates the elements of **study design** and **aggregate quality** of the studies under consideration.
- *GRADE:* **Study quality** and **study design** are key elements.
- *USPSTF:* The following questions are considered while grading the evidence:
  - "To what extent are the existing studies of high quality? (i.e., what is the internal validity?)"
  - "Do the studies have the appropriate research design to answer the key question(s)?"

C. Inconsistency or Unknown Consistency

In the EPC SOE system, consistency is defined as the degree to which reported effect sizes from included studies appear to go in the same direction.[18] The two elements are whether effect sizes have the same sign (same side of "no effect") and whether the range of effect sizes is narrow.[18] According to the GRADE system, consistency refers to the similarity of estimates of effect across studies, incorporating direction of effect, size of differences in effect, and the significance of the differences in effect size.[19] However, it should be kept in mind that a statistically significant effect size in one study and an effect size whose confidence interval overlaps null in another study do not necessarily constitute inconsistent results. If there is only one available study, even if considered large sample size, the consistency of results is unknown.[18]

Correspondence to grading systems:

- *EPC SOE:* Consistency is a required domain.
- *GRADE:* Consistency is a key element.
- *USPSTF:* The following question is considered while grading the evidence:
  - "How consistent are the results of the studies?"

D. Not the Right Information

There are a number of reasons why identified studies might not provide the right information. First, results from studies might not be applicable to the population and/or setting of interest. Second, the optimal or most important outcomes might not be assessed. For example, studies might only include surrogate or intermediate outcomes. Third, the study duration might be too short and patients might not be followed up for long enough duration to adequately assess some outcomes which might be most important.

Correspondence to grading systems:

- *EPC SOE:* **Applicability** is as an 'other pertinent issue'. **Directness** is a required domain. It also incorporates the element of surrogate versus clinical outcomes.
- *GRADE:* **Directness** is a key element, incorporating the elements of applicability and surrogate versus clinical outcomes.
- *USPSTF:* The following question is considered while grading the evidence:
  - "To what extent are the results of the studies generalizable to the general U.S. primary care population and situation? (i.e., what is the external validity?)"

Characterization of Research Gaps

To further characterize the research gaps we propose using the PICOS framework using the population (P), intervention (I), comparison (C), outcomes (O), and setting (S). Those elements which are inadequately addressed in the evidence base should be characterized. The other relevant elements will be apparent from the key question from which the research is derived. It follows that for research questions that do not relate to a specific key question, all available elements of the research gap should be characterized.

Population (P)

Information here should be as specific as possible as to the age, sex, race/ethnicity, clinical stage, etc. of the population that is not adequately represented in the evidence base. However, it should be recognized that research gaps often do not relate to any specific population but refer to the general population.

Examples of populations include: women with gestational diabetes, adults on anti-depressive medication, and African Americans with *Helicobacter pylori* infection.

Intervention (I)

The specific name of the intervention that is inadequately included in the evidence base (generic names of drugs and devices are preferred), the duration of the intervention, its dose, its frequency, who will administer it, etc. should be specified. As with the population, it may not always be appropriate to specify great detail about the intervention.

Examples of interventions include: metformin, selective serotonin reuptake inhibitors (SSRIs), any oral antihistaminic drug, and total thyroidectomy.

Comparison (C)

The same relevant details about the comparative intervention should be specified as for the intervention of interest – name of comparative intervention, its duration, its dose, its frequency, who will administer it, etc. If the comparison is "any other intervention," this should be indicated. Similarly, if the comparison is "no intervention" or placebo, it should be specified as such. It should also be recognized that there may be instances where there is no specific comparison of interest.

Examples of comparisons include: any insulin, any non-steroidal anti-inflammatory drug (NSAID), hemithyroidectomy, and placebo.

Outcomes (O)

It may be appropriate to organize outcomes by type of outcomes or to only list the types of outcomes (e.g., maternal outcomes and fetal outcomes, liver outcomes, and renal outcomes). If

appropriate, the timing of outcome assessments that are missing should be specified (e.g., body mass index [BMI] at 12 months, 5-year survival rate). If there are no specific outcomes of interest, this should be indicated.

Examples of outcomes include: neonatal hypoglycemia, neonatal intensive care unit (NICU) admissions; liver outcomes (alanine transaminase [ALT], aspartate transaminase [AST]); and renal outcomes (proteinuria, serum creatinine).

Setting (S)

Where appropriate, members should specify the relevant settings for research gaps.

Examples of settings include: at home, in the hospital, in the outpatient setting, in the United States.

Special Considerations

In addition to characterizing research gaps that relate to treatment interventions, the PICOS framework can be used to characterize gaps that relate to diagnostic tests, clinical assessments, and screening tests. These are described below.

Research gaps relating to the accuracy of diagnostic tests can be fit into the PICOS framework by considering the diagnostic test under investigation as the intervention (I) and the gold or reference standard test as the comparison (C). Relevant outcomes (O) in this case could include sensitivity, specificity, and other metrics of test performance.

Research gaps relating to the benefit of one form (or frequency) of clinical assessment (e.g., monitoring) versus another can be fit into the PICOS framework by considering these clinical assessments as intervention (I) and comparison (C). The comparison in this case could include a standard form (or frequency) of clinical assessment or no clinical assessment. Relevant outcomes (O) could include clinical outcomes to assess the benefit of the clinical assessment(s).

Research gaps relating to screening tests can be fit into the PICOS framework by considering these tests as intervention (I) and comparison (C). Relevant outcomes (O) could include clinical outcomes to assess the benefit of the screening test(s).

Research gaps which are difficult to characterize into the PICOS framework should be abstracted in free text form. Interventions could potentially include a range of treatment options, order of treatment options, individualization of treatments, etc. These are often gaps for which it is difficult to identify a clear intervention or comparison of interest. Examples of research questions derived from such research gaps are: “What are the optimal glucose thresholds for medication use in women with gestational diabetes?”; “In what order should patients with cystic fibrosis perform their airway clearance therapies?” and “How should physicians choose an airway clearance therapy for a given patient with cystic fibrosis?”

Worksheet

Using the above described framework, we designed a worksheet to facilitate the identification and organization of research gaps during evidence reviews sponsored by AHRQ (see Table 5). Our aim was to design a simple, user-friendly worksheet to help investigators record research gaps. We envision that investigators would fill out this worksheet soon after the data synthesis phase, while in the process of writing the results section of the evidence report. Having just completed reviewing the evidence in detail, we believe that this is the ideal time for investigators to comprehensively and accurately identify individual research gaps. See

Appendixes E and F for the research gaps characterization worksheet and instructions for its completion, respectively.

Table 5. Step 4: Development of framework—Research gaps abstraction worksheet

<Project Name>
Research Gap Worksheet
Page ____ of ____
Key Question Number – _____

Completed by – _____
Date – _____

Serial No.	Reason(s) for Gap*	Population (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Setting (S)	Free Text of Gap	Notes
Example	B	Women with gestational diabetes	Metformin	Any insulin	Neonatal hypoglycemia, NICU admissions	-		-
Example	D	-	-	-	-		How should the physician assess asthma or bronchodilator responsiveness?	

***** Reasons for Gap:
A. Insufficient or imprecise information
B. Biased information
C. Inconsistency or unknown consistency
D. Not the right information.

The use of a worksheet may be beneficial in two main ways. First, it facilitates the use of a systematic process in identifying and recording research gaps during systematic reviews. This would also facilitate the discussion about research gaps between team members who might have written the results for different key questions. Second, the worksheet would enable investigative teams to write the future research section of an evidence report in a more organized and systematic manner. A proposed format for presenting research gaps in evidence reports is provided in the discussion section of this report.

Step 5: Pilot Test of Framework

We pilot tested our framework on two randomly selected evidence reports not produced by our EPC.[17,21] The average time taken to abstract research gaps was 3.5 hours per evidence report. On average, there were 14.75 research gaps identified per evidence report. On average, there were 2 (13.6%) research gaps per evidence report which could not be characterized using the PICOS framework. These research gaps did not relate to a specific intervention or comparison, but instead related to prevalence, incidence, and the effect of certain factors on prevalence and incidence. These research gaps were thus abstracted in free text form.

Challenges To Use of Framework

We encountered a few challenges when pilot testing the framework. First, the average time taken to pilot test the framework was 3.5 hours per evidence report. This task was challenging predominantly because we were not involved with the conduct of the evidence reviews or the writing of their results. Completing the task often necessitated reading the background and methods of the report including details about the key questions themselves. It would likely be more efficient if this task is completed by the same team that completed the systematic review.

Second, only one of the two evidence reports that we used to pilot test our framework included a "strength of evidence" (SOE) table for each question of interest. If this table is adopted by investigative teams, they can leverage work that would already have been done in the completion of the table to identify research. According to this AHRQ-recommended evidence grading system, the overall strength of the evidence is graded as "high," "moderate," "low," and "insufficient,"[18] If the overall evidence is graded as "moderate," "low," or "insufficient" it is subjectively implied that further research at least may change our confidence in the estimate or may change the estimate itself.[18] Research gaps can thereby be identified as topics or areas for which further research may change our conclusions (i.e., those graded as "moderate," "low," or "insufficient" strength of evidence using the AHRQ-recommended evidence grading system).

Third, the two research team members who carried out the pilot test often chose two different reasons for gaps when only one study was identified. These reasons were: A. insufficient information and C. unknown consistency. It was not decided beforehand what reason for gap would be selected if such gaps were identified.

Fourth, the two research team members also abstracted a different number of gaps because of differences in the specificity of the research gaps. It was not decided beforehand whether gaps should be abstracted at the key question level or at the level of specific comparisons (subquestions) within key questions. This was particularly an issue whenever no studies were identified for key questions with more than one specific comparison.

Similarly, when comparing the results of our pilot test with the future research sections of the evidence reports, the research gaps we identified were more specific. This arose because we identified each intervention and comparison as a separate research gap, while the authors of the

evidence report tended to group together groups of interventions and comparisons. For example, two of our research gaps were related to the use of decision aids and physician reminders to improve the appropriate use of colorectal cancer screening. However, in the future research section of the evidence report, the authors were more general and suggested the development and testing of "promising interventions that need more research especially integrated with other practice systems and especially in combinations".[21]

Fifth, as described above, some research gaps could not be abstracted using the framework and needed to be abstracted in free text form.

Step 6: Refinement and Finalization of Framework

Changes to the framework and the worksheet at this stage only involved minor formatting and clarification of instructions.

Discussion

We utilized multiple resources and perspectives including literature review, contact with other EPCs and organizations involved with evidence synthesis, and consultation with experts at our institution to develop a framework for the identification and characterization of research gaps. This framework involves two main components – identifying explicitly why the research gap exists and characterizing the research gap using widely accepted key elements. This framework facilitates the use of a systematic method to identify research gaps.

Strengths

There are important strengths to the process we used to achieve our objective. First, our process utilized multiple resources and perspectives. These included a focused literature review and consultation with twelve other EPCs, thirty-seven organizations from around the world which are involved with evidence synthesis, and two technical experts from our institution. Second, we pilot tested the use of the framework on two randomly selected AHRQ evidence reports. This pilot test did not identify any major problems with the framework but did identify the need for consistency and prior decisionmaking on the part of investigative team members.

There are several strengths to the framework itself. First, it is based on widely accepted key elements (PICOS) of a well-designed research question. AHRQ also recommends that EPCs use the PICO elements during the topic refinement process. Second, the use of these elements will potentially make the process of identification of research gaps more systematic and therefore useful. Third, for each underlying reason for research gap we have provided the corresponding domain/element in three common evidence grading systems (the EPC SOE system, the GRADE system, and the USPSTF grading system). We anticipate that this will enhance the use of this framework by leveraging work already being completed. Finally, in addition to indicating *where* the current evidence falls short, the framework also indicates *why* the evidence falls short (reasons for existence of research gaps). Knowing where the gaps are and the reason(s) underlying their existence could help in the design of the appropriate research to fill them.

The worksheet is simple to use and facilitates the presentation of research gaps. It is transparent and reproducible. A proposed format for presenting research gaps is provided below.

Proposed Format for Presenting Research Gaps and Research Questions

We did not find consistency in how research gaps were presented during our audit of the evidence reports. Some reports presented these by embedding them in text while others used bullet-point lists, numbered lists, or presented as tables.

We propose that while writing the future research needs sections of evidence reports, investigative teams provide adequate details of research gaps and translate them into research questions. While translating gaps into research questions, all relevant PICOS elements should be incorporated. This would ensure that such questions are stand-alone and can be more effectively used by those designing research agendas. We propose that EPCs use the following format for presenting research gaps in evidence reports:

- Key Question Number and Key Question Topic
  - Research Gap Number
    - Reason for Gap
    - Population (P)
    - Intervention (I)
    - Comparison (C)
    - Outcomes (O)
    - Setting (S)
  - Research Question.

Evidence reports often identify research gaps which do not relate to any specific key question. Such research gaps could be presented at the end of the future research section. We suggest use of the same format as above, but Key Question Number and Key Question Topic would be replaced by "Other Research Gaps".

An example of presenting two research gaps and translated research questions is provided below:

- Key Question I – What are the risks and benefits of oral diabetes agents (e.g., second-generation sulfonylureas and metformin) as compared to all types of insulin in women with gestational diabetes?
  - Research Gap Number 1
    - Reason for Gap – biased information (randomized trials not identified)
    - Population (P) – women with gestational diabetes
    - Intervention (I) – metformin
    - Comparison (C) – any insulin
    - Outcomes (O) – neonatal hypoglycemia and NICU admissions
    - Settings (S) – any setting
  - Research Question Number 1: What is the effectiveness of metformin compared to any insulin in reducing neonatal hypoglycemia and NICU admissions in women with gestational diabetes?
  - Research Gap Number 2
    - Reason for Gap – insufficient information (sample sizes in studies too small)
    - Population (P) – women with insulin-requiring (type A2) gestational diabetes at 40 weeks of gestation
    - Intervention (I) – elective labor induction
    - Comparison (C) – expectant management
    - Outcomes (O) – emergency cesarean delivery (maternal) and macrosomia (neonatal)
    - Settings (S) – any setting
  - Research Question Number 2: What is the effectiveness of elective labor induction compared to expectant management in preventing emergency cesarean delivery and neonatal macrosomia in women with insulin-requiring (type A2) gestational diabetes at 40 weeks of gestation?

Limitations and Future Research

We identified limited use of formal processes, including frameworks, for identifying research gaps. This prevented us from answering subquestions 1.b. and 1.c. as we were unable to compare existing methods for identifying and presenting research gaps. Further refinement of the framework we propose, and development of other frameworks, would allow future research to assess relative usefulness of different frameworks.

A limitation of the framework that we have developed is that it does not explicitly account for the specificity of research gaps. Team members could differ in terms of the number of research gaps abstracted based on whether gaps are abstracted at the level of the key question or the subquestion. We therefore suggest that *a priori* decisions be made about the level of specificity that should be accomplished and that investigative teams be consistent. This decision would likely depend upon the topic of interest as well as the specific intervention and comparison. The benefit of being specific needs to be weighed against the time required and the need to identify each specific intervention and comparison of interest.

In identifying research gaps we suggest that investigative teams be consistent and decide *a priori* about the specificity of research gaps to be identified and presented. It is also important to be consistent and decide *a priori* which reason will be selected when the gap arises because only one study is identified (i.e., insufficient information or unknown consistency). While identifying reasons why a research gap exists, team members must remember to pick the main reason(s) that prevents conclusions from being made and to be as specific as possible. This would potentially help towards designing the appropriate research to fill that gap.

Our framework calls for identifying the most important reason(s) for existence of research gaps (i.e., reasons that most preclude conclusions from being made). However, there may often be more than one main reason why a research gap exists. Team members could differ on the relative importance of these reasons. Decisions on the relative importance of these reasons are often arbitrary. More research is needed to determine if a hierarchy or ranking system can be established to aid these decisions.

The application of the framework to identify research gaps by our investigative team was quite challenging. Much of this was due to our team being unfamiliar with the evidence reports and trying to retrospectively apply the framework. We suggest that the same investigative team which synthesizes the evidence apply the framework while writing the results. We also suggest that investigative teams working on evidence reports use the SOE for grading the evidence. If this is done, teams can leverage work done in preparing the table to identify research gaps.

Our pilot test relied on applying the worksheet retrospectively on existing evidence reports. Further evaluation is needed to see how the framework performs with other types of reports or questions. Evaluation is needed to determine if the gaps identified using the framework are different than those identified using current methods. This could be assessed by examining the number of gaps identified, the perceived usefulness of the gaps, as assessed by potential stakeholders (usefulness could be further defined as actionable gaps, important gaps, etc.). Future research could have other EPCs use the worksheet during the drafting of an evidence report. Another evaluation could have some members of an EPC team use the worksheet, and others not, to compare the process and outcome (i.e., future research section). Further, the format for presentation of the research gaps could be evaluated for clarity and ease of use by other EPCs as well as by other relevant stakeholders, including researchers and funders.

Conclusions

We searched the literature, conducted an audit of EPC evidence reports, and sought information from other organizations that are involved with evidence synthesis. Despite these efforts, we identified little detail or consistency in the frameworks used to determine research gaps within systematic reviews. In general, there is no widespread use or endorsement of a specific formal process or framework for identifying research gaps using systematic reviews.

We developed a framework to facilitate the systematic identification of research gaps through the classification of where the current evidence falls short and why the evidence falls short. A worksheet was developed to facilitate the use of the framework when completing a systematic review and thus facilitate the use of a systematic process to identify research gaps.

References

1. Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009;10(2):147-159.
2. Shepherd J, Briggs J, Payne L, et al. Setting the future policy agenda for health technology assessment: a specialty mapping approach. Int J Technol Assess Health Care 2007;23(4):405-413.
3. Clarke L, Clarke M, Clarke T. How useful are Cochrane reviews in identifying research needs? J Health Serv Res Policy 2007;12(2):101-103.
4. Johnson NP, Proctor M, Farquhar CM. Gaps in the evidence for fertility treatment-an analysis of the Cochrane Menstrual Disorders and Subfertility Group database. Hum Reprod 2003;18(5):947-954.
5. de Vet HC, Kroese ME, Scholten RJ, et al. A method for research programming in the field of evidence-based medicine. Int J Technol Assess Health Care 2001;17(3):433-441.
6. Seidenfeld J, Samsom DJ, Rothenberg BM, et al. HER2 testing to manage patients with breast cancer or other solid tumors. Evid Rep Technol Assess (Full Rep) 2008;(172):1-362.
7. Myers ER, McCrory DC, Mills AA, et al. Effectiveness of assisted reproductive technology (ART). Evid Rep Technol Assess (Full Rep) 2008;(167):1-195.
8. Marchionni L, Wilson RF, Marinopoulos SS, et al. Impact of gene expression profiling tests on breast cancer outcomes. Evid Rep Technol Assess (Full Rep) 2007;(160):1-105.
9. Complementary and alternative medicine in back pain utilization report. Evid Rep Technol Assess (Full Rep) 2009;(177):1-221.
10. Jimison H, Gorman P, Woods S, et al. Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved. Evid Rep Technol Assess (Full Rep) 2008;(175):1-1422.
11. Viswanathan M, Siega-Riz AM, Moos MK, et al. Outcomes of maternal weight gain. Evid Rep Technol Assess (Full Rep) 2008;(168):1-223.
12. Shekelle PG, Newberry S, Maglione M, et al. Bariatric surgery in women of reproductive age: special concerns for pregnancy. Evid Rep Technol Assess (Full Rep) 2008;(169):1-51.
13. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess (Full Rep) 2009;(183):1-420.
14. Couch R, Jetha M, Dryden DM, et al. Diabetes education for children with type 1 diabetes mellitus and their families. Evid Rep Technol Assess (Full Rep) 2008;(166):1-144.
15. Butler M, Kane RL, McAlpine D, et al. Integration of mental health/substance abuse and primary care. Evid Rep Technol Assess (Full Rep) 2008;(173):1-362.
16. Tsertsvadze A, Fink HA, Yazdi F, et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med 2009;151(9):650-661.
17. Hartmann KE, McPheeters ML, Biller DH, et al. Treatment of overactive bladder in women. Evid Rep Technol Assess (Full Rep) 2009;(187):1-120, v.
18. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010;63(5):513-523.
19. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490.

20. Sawaya GF, Guirguis-Blake J, LeFevre M, et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med 2007;147(12):871-875.

21. Holden DJ, Harris R, Porterfield DS, et al. Enhancing the use and quality of colorectal cancer screening. Evid Rep Technol Assess (Full Rep) 2010;(190):1-195, v.

Abbreviations

AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery Foundation
ACP	American College of Physicians
AETS	Agencia de Evaluación de Tecnologias Sanitarias
AETSA	Andalusian Agency for Health Technology Assessment
AETMIS	Agence d'évaluation des technologies et des modes d'intervention en santé (Québec Government Agency responsible for Health Services and Technology Assessment)
Age.na.s	The Agency for Regional Healthcare
AGREE	Appraisal of Guidelines Research and Evaluation
AHMAC	Australian Health Ministers Advisory Council
AHRQ	Agency for Healthcare Research and Quality
AHTA	Adelaide Health Technology Assessment
AHTAPol	Agency for Health Technology Assessment in Poland
ALT	Alanine Transaminase
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures--Surgical
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
AUA	American Urological Association
AVALIA-T	Galician Agency for Health Technology Assessment
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CAHIAQ	Catalan Agency for Health Information, Assessment and Quality
CARI	Caring for Australasians with Renal Impairment
CCE	Centre for Clinical Effectiveness
CCO	Cancer Care Ontario
CDE	Center for Drug Evaluation
CEA	Cost-Effectiveness Analysis
CEDIT	Comité d´Evaluation et de Diffusion des Innovations Technologiques
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud
CER	Comparative Effectiveness Review
CIR	Center for International Rehabilitation
CMS	Center for Medicare and Medicaid Services
CNHTA	Committee for New Health Technology Assessment
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CORE	Centralized Otolaryngology Research Efforts
CRD	Center for Reviews and Dissemination
CVZ	College voor Zorgverzekeringen
DACEHTA	Danish Centre for Evaluation and HTA

DAHTA@DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information
DECIT-CGATS	Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia
DRI	Dietary Reference Intake
DSEN	Drug Safety and Effectiveness Network
DSI	Danish Institute for Health Services Research
DUETS	Database of Uncertainties about the Effects of Treatments
EPC	Evidence-based Practice Center
ETESA	Department of Quality and Patient Safety of the Ministry Health of Chile
FDA	Food and Drug Administration
FinOHTA	Finnish Office for Health Technology Assessment
GDG	Guideline Development Group
G-I-N	Guidelines International Network
GmBH	Gesellschaft mit Beschränkter Haftung
GÖG	Gesundheit Österreich GmbH
GR	Gezondheidsraad
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HER2	Human Epidermal growth factor Receptor 2
HIQA	Health Information and Quality Authority
HITAP	Health Intervention and Technology Assessment Program
HSAC	Health Services Assessment Collaboration
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICTAHC	Israel Center for Technology Assessment in Health Care
IECS	Institute for Clinical Effectiveness and Health Policy
IHE	Institute of Health Economics
INAHTA	International Network of Agencies for Health Technology Assessment
IOM	Institute of Medicine
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IT	Information Technology
JBI	Joanna Briggs Institute
JHU EPC	Johns Hopkins University Evidence-based Practice Center
KCE	Belgian Health Care Knowledge Centre
KDOQI	Kidney Disease Outcomes Quality Initiative
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment
MaHTAS	Health Technology Assessment Section, Ministry of Health Malaysia
MAS	Medical Advisory Secretariat
MSAC	Medical Services Advisory Committee
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health
MUMM	Managed Uptake of Medical Methods
NBOCC	National Breast and Ovarian Cancer Centre
NETSCC, HTA	NIHR Coordinating Centre for Health Technology Assessment
NHSC	National Horizon Scanning Center

NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NKF	National Kidney Foundation
NOKC	Norwegian Knowledge Centre for the Health Services
NSAID	Non-Steroidal Anti-Inflammatory Drug
OSTEBA	Basque Office for Health Technology Assessment
PEBC	Program in Evidence-based Care
PICO	Population, Intervention, Comparison, and Outcomes
PICOS	Population, Intervention, Comparison, Outcomes, and Setting
QIS	Quality Improvement Scotland
RAB	Research Advisory Board
RAND	Research And Development
RCN	Royal College of Nursing
RCT	Randomized Controlled Trial
RFA	Request For Applications
RTI	Research Triangle Institute
SBU	The Swedish Council on Technology Assessment in Health Care
SCHIP	State Children's Health Insurance Program
SIGN	Scottish International Guidelines Network
SSRI	Selective Serotonin Reuptake Inhibitor
STI	Sexually Transmitted Infection
TA	Technology Assessment
TEP	Technical Expert Panel
UETS	Unidad de Evaluación de Tecnologías Sanitarias
UK	United Kingdom
UNC	University of North Carolina
US	United States
USPSTF	United States Preventive Services Task Force
UVT	HTA Unit in A. Gemelli Teaching Hospital
VA	Veterans Affairs
VASPVT	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania
VATAP	Veterans Affairs Technology Assessment Program
ZonMw	The Medical and Health Research Council of The Netherlands

Appendix A. AHRQ's Seven Questions About the Development, Prioritization, and Presentation of Research Needs

1. Define frameworks for determining research gaps conducted within a systematic review.
   - What are the various frameworks (concepts and organizing principles) used to determine the research gaps within a systematic review? (Research gaps are defined as missing evidence which limited the ability of reviewer to reach a conclusion for the given question.)
     - How often do the identified gaps extend beyond the reach of the original key questions?
   - Is there any evidence that one method for identifying research gaps is more valid than another?
   - Is there any evidence that one format for presenting research gaps is more useful than another?

2. Finding evidence on ongoing studies.
   - How can EPCs find information on currently ongoing studies?
     - What databases are available for searching?
     - Are there efficient methods for searching these databases?
     - What is the incremental benefit of additional grey literature searches?

3. Identify methods and processes for engaging stakeholders to define and prioritize research needs (i.e., decision-makers, researchers, funders).
   - What methods can be used to gather stakeholder input (individual calls, group calls/web-ex, in-person meetings etc.)?
     - What are the tradeoffs of each method?
     - Is one method is more useful for a certain type of question?
   - What methods can be to collate the stakeholder input (delphi, consensus, etc.)?
     - What are the tradeoffs of each method?
     - Is one method is more useful for a different purpose?

4. Define criteria for prioritizing research gaps to research needs.
   - What criteria do stakeholders use to prioritize research gaps?
     - Are they different for different stakeholders?
     - Are they different for different questions?
   - How can information be organized to facilitate stakeholder input?

5. Determine appropriate uses of modeling or VOI.
   - Describe different modeling or VOI methods that could be used for developing and prioritizing research gaps from systematic reviews.
     - What methods have been used?
     - What information is needed to such conduct modeling or VOI methods?
     - How can they be adapted to EPC purposes?
   - Is there any evidence that one method is more valid or useful than others?

6. Define an optimal format for presenting research needs.
    - What level of specificity is needed by various funders for a Research needs document to be useful?
        - Description of project design – i.e., study design, PICO questions, sample size
        - Background and justification of prioritized list.
    - How can research needs be categorized and presented?
        - Is there any evidence that one organization schema is preferred over another?
    - What are barriers to making a Research needs document useful to researchers and funders?

7. Assess the impact of developing Research Needs documents.
    - What is the current impact of the EPC program on currently funded studies?
    - How will development of Research Needs documents change the impact of the EPC program on funded studies?

Appendix B. Step 2: Review of Current Practices of Evidence-based Practice Centers (EPCs)—Data Abstraction Form for Audit of Evidence Reports

Sr. No.	Were Research Gaps/Needs Defined?	Was There a Description of How Research Gaps/Needs Were Identified?	Was There an Explicit Framework/Set of Organizing Principles (e.g., PICO, a Diagram) Used for the Identification of Research Gaps/Needs?	Were Future Research Gaps/Needs Provided in the Report?	Were Future Research Gaps/Needs Provided as a Part of the Discussion Section?	If Future Research Needs/Gaps Were ONLY Described in the Discussion and NOT in the Methods, Was There a Description (in the Results) of How They Were Identified?	How Were Research Gaps/Needs Presented? (INDICATE ALL WAYS PRESENTED)
1							
2							
3							
4							
5							
6							

Abbreviations: EPC=evidence-based practice center, PICO=population, intervention, comparison, and outcomes.

Appendix C. Step 2: Review of Current Practices of Evidence-based Practice Centers (EPCs)—Responses Obtained From EPCs

EPC #	EPC Name	Title of Evidence Report (Ref No.)	Question: Did You Use a Specific Framework or Method To Identify Research Gaps? If so, Please Describe the Method Below.	Question: Do You Have Any Corrections or Clarifications on What Was Abstracted? If so, Please List Them Below.	Question: Have You Implemented a Different Process Since Publishing the Above-Mentioned Report? If so, Please Provide a Description of the Process, and Indicate When it Was Implemented.
1	Blue Cross and Blue Shield Association	HER2 testing to manage patients with breast cancer or other solid tumors[6]	No	I am not sure what you mean in your table by "were research gaps defined?" We did not define the term research gap, but we did identify specific research gaps through the report. They were often embedded in the test or implicit, however. For example, when a key question cannot be answered because of poor or heterogeneous evidence, it is implicit that a research gap exists; see, e.g., the conclusions to key question 5 on p. 155. That being said, having a more explicit list of research gaps would be useful and advisable. Much of the weakness of the evidence in this report had to do with methodological issues. For example, did studies that relied on banked samples from prior RCTs adequately address the issue of missing samples and any bias that might result (e.g., was the percentage of HER2 positive patients similar in both arms of the trial for which there were samples?). Also, few studies used appropriate multivariable analysis and then tested for an interaction terms between HER2 status and treatment group. The description of the methods used was often scanty and precluded determination of whether this has been done. Therefore, much of Chapter 4, Discussion and Future Research, focused on these methodological issues that greatly undermined confidence in the existing studies.	We have not adopted a specific framework like PICOS in more recent completed repots, but we have become more explicit in grading the quality of evidence for each key question (implicitly indicating where the research gaps exist) and in providing a concise list of research recommendations. This change began with the CER on radiotherapy techniques in head and neck cancer, the report that followed HER2 and was recently released publicly. With AHRQ's emphasis in the ARRA work and our pilot project on future research on treatments for localized prostate cancer, we are developing explicit lists of research gaps, organized using PICOS, and recommended research, and relying on a multidisciplinary panel to rank them.

EPC #	EPC Name	Title of Evidence Report (Ref No.)	Question: Did You Use a Specific Framework or Method To Identify Research Gaps? If so, Please Describe the Method Below.	Question: Do You Have Any Corrections or Clarifications on What Was Abstracted? If so, Please List Them Below.	Question: Have You Implemented a Different Process Since Publishing the Above-Mentioned Report? If so, Please Provide a Description of the Process, and Indicate When it Was Implemented.
2	Duke University EPC	Effectiveness of assisted reproductive technology[7]	No, we didn't use a specific framework or methodology. The general approach to identifying research gaps for the reports has been to summarize (1) the existence of relevant literature addressing the key questions (a major problem for many women's health issues), and (2) methodological issues in the existing literature which contribute to uncertainty. Within the range of research gaps identified for a particular question, we have not used any formal methods for prioritization.	The abstraction appears correct.	No
3	Johns Hopkins University EPC	Impact of gene expression profiling tests on breast cancer outcomes[8]	No	No	No
4	McMaster University EPC	Complementary and alternative medicine in back pain utilization report[9]	This question was not included (a framework was identified).	The summary above is generally correct. You raise an excellent point regarding specifying what is or is not a "research gap." It will be interesting to see how others identify these.	We do not seem to be consistent across reviews in the location or methods of reporting research gaps, other than consistently locating these within the discussion.

EPC #	EPC Name	Title of Evidence Report (Ref No.)	Question: Did You Use a Specific Framework or Method To Identify Research Gaps? If so, Please Describe the Method Below.	Question: Do You Have Any Corrections or Clarifications on What Was Abstracted? If so, Please List Them Below.	Question: Have You Implemented a Different Process Since Publishing the Above-Mentioned Report? If so, Please Provide a Description of the Process, and Indicate When it Was Implemented.
5	Oregon EPC	Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved[10]	The authors presented an analytic framework for separating research questions (and studies) into 5 categories. Many studies focused on the earlier relationships in the model (Patient Characteristics, Environment, and Technology influencing the use of Health IT). Other studies had information on the subsequent relationship between Health IT use and process outcomes (health behaviors, self-efficacy, physiological measures). There were very few studies that looked at the final outcomes of quality-of-life, satisfaction, and costs. The lack of information in existing studies to answer each of the component research questions, with respect to the elderly, underserved and chronically ill, defined the research gap.In addition, many gaps/issues arose as we reviewed the material (e.g., need is for a principled taxonomy of interactive Health IT interventions, best practices for the design and implementation, etc.). Finally, there were summaries at the end of the analysis of each research question. These summaries usually identified that there was insufficient research in that area on disadvantaged populations, such as minorities, low-income groups, elderly, disabled, and geographically remote populations.	Yes. The information included in a table is as follows: - Were research gaps defined? Ch. 5 described and defined the research gaps. In addition, at the end of the summary of each of the 5 research questions, unanswered questions were identified. - Was there a description of how research gaps/ needs were identified? The lack of information in existing studies to answer each of the component research questions from the analytic framework, with respect to the elderly, underserved and chronically ill, defined the research gap. In addition, many gaps/issues arose as we reviewed the material (e.g., need is for a principled taxonomy of interactive Health IT interventions, best practices for the design and implementation, etc.). - Was there an explicit framework/ set of organizing principles (e.g. , PICO, a diagram) used for the identification of research gaps/needs? The authors presented an analytic framework for separating research questions (and studies) into 5 categories. Many studies focused on the earlier relationships in the model (Patient Characteristics, Environment, and Technology influencing the use of Health IT). Other studies had information on the subsequent relationship between Health IT use and process outcomes (health behaviors, self-efficacy, physiological measures). There were very few studies that looked at the final outcomes of quality-of-life, satisfaction, and costs. The lack of information in existing studies to answer each of the component research questions, with respect to the elderly, underserved and chronically ill, defined the research gap.	No

EPC #	EPC Name	Title of Evidence Report (Ref No.)	Question: Did You Use a Specific Framework or Method To Identify Research Gaps? If so, Please Describe the Method Below.	Question: Do You Have Any Corrections or Clarifications on What Was Abstracted? If so, Please List Them Below.	Question: Have You Implemented a Different Process Since Publishing the Above-Mentioned Report? If so, Please Provide a Description of the Process, and Indicate When it Was Implemented.
5 (cont.)	Oregon EPC (cont.)	Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved[10] (cont.)		- Were future research gaps/ needs provided, and where were they found? Ch. 5 described and defined the research gaps. In addition, at the end of the summary of each of the 5 research questions, unanswered questions were identified. There was an additional section in the Executive Summary describing research gaps. Executive Summary Research Gaps: Questions remain as to (a) the optimal frequency of use of the system by the patient, which is likely to be condition-specific; (b) the optimal frequency of use or degree of involvement by the health professionals; (c) whether their success depends on repeated modification of the patient's treatment regimen or simply ongoing assistance with applying a static treatment plan. However, it is clear that the consumer's perception of benefit, convenience and integration into daily activities will serve to facilitate the successful use of the interactive technologies for the elderly, chronically ill, and underserved. Perhaps most challenging, these systems shift the locus of care away from traditional physician office visits, and many of them involve the participation of a multidisciplinary health care team; these activities are difficult to support financially under current episode-based, fee-for-service health care reimbursement mechanisms. Chapter 5 Research Gaps:In our review of the evidence on the barriers and drivers of the use of interactive consumer health IT by the elderly, chronically ill, and underserved populations we identified several areas for future work. The most	No

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5 (cont.)	Oregon EPC (cont.)	Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved[10] (cont.)		pressing need is for a principled taxonomy of interactive consumer health IT and related interventions, so that the resulting outcomes of studies involving these systems can be better interpreted by understanding effects of the various components. Currently, it is difficult to generalize across the wide variety of systems. Similarly, future research is needed to understand best practices for the design and implementation of these interactive health technologies for patients. A clear taxonomy will facilitate this effort. In addition to standardizing our descriptions of the variety of interactive consumer health IT applications, it will be important to develop standardized and clear definitions of the intermediate outcomes relating to the use of these technologies. For example, in the studies we reviewed, system usage has been measured by logins, Web clicks, or time within a session. These varied measures, along with differing expectations for use for each system, make it difficult to compare usage between systems in a meaningful way. The issue gains relevance as the field strives to determine if the measurement of the health technology usage can serve as a means of determining individual engagement, activation, or preference, and whether it can serve as a proxy for intervention exposure or "dose."	No

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5 (cont.)	Oregon EPC (cont.)	Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved[10] (cont.)		Finally, there is a paucity of research with direct comparison of the use and outcomes of these technologies by the general population versus disadvantaged populations, such as minorities, low-income groups, elderly, disabled, and geographically remote populations. It would be very useful to test the same technology, protocol, and implementation interventions with comparison populations within the same study, to truly understand the barriers and drivers associated with these interventions. Summary at the end of each Research Question: These summaries usually identified that there was insufficient research in that area on disadvantaged populations, such as minorities, low-income groups, elderly, disabled, and geographically remote populations.	

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6	RTI International - UNC EPC	Outcomes of maternal weight gain[11]	No, we didn't have a formal framework that we used. Informally, we used the "limitations of the evidence base" section to identify methodological areas for future research and the key questions to identify areas for future research for content-specific topics.	No	I think that we are continuing to use the two-step process described above – that is, we use the methods limitations to construct methodological areas for improvement, and the key questions to identify content-specific areas for future research. One change is that the PICOS framework has been more rigorously applied in each generalist review (they are already embedded in our CERs), so the questions and the areas for future research in our generalist reviews might reflect PICOS better now that they had in the past. Having said that, we are not explicit in our use of PICOS for the future research needs section. Another change is that we now include a summary of strength of evidence in the discussion chapter for generalist reviews that shows where there is no evidence (or insufficient evidence) so it's more apparent to the reader where we came up with the content-specific gaps.

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7	Southern California/ RAND EPC	Bariatric surgery in women of reproductive age: Special concerns for pregnancy[12]	I'm not sure a specific "framework" is needed. We were given key questions to investigate, included PICOS. If no evidence is found to address a specific issue / PICO, and no studies are underway to address the issue, then clearly a research gap exists. Same goes for if only low quality evidence exists. We usually run the "future research" suggestions by the TEP for input and additional suggestions. We can certainly add a few sentences in future reports on the process. However, this is not rocket science. I don't think we need to waste resources (i.e., tax dollars) creating some fancy algorithm or official process.	Again, I never found it necessary to define the term "research gap" because I felt it was more than obvious to the reader.	No, same process as listed above. Again, we could add a one paragraph description to the methods section of future reports. We do look at each key question, population, intervention, and outcome to see where research gaps exist. This can easily be done with an excel table; I don't think we need to spend a lot of time creating some complex process.

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8	Tufts University EPC	Vitamin D and calcium: A systematic review of health outcomes[13]	Please see answer to next question.	Vitamin D and Calcium: Systematic Review of Health Outcomes report was not a good example of typical AHRQ evidence reports that would represent that practices of our center used to identify or present research gaps. This report was commissioned to support the development of Dietary Reference Intake (DRI) values. DRIs are the nutrient reference values issued by the Institute of Medicine (IOM) of the National Academy of Sciences and we followed a previously established framework which was designed to facilitate the decision-making process of an expert panel of IOM. For this reason, there was no typical " Future Research" section in this report. One of the objectives of this report was to help IOM panel to identify research gaps deriving vitamin D and calcium DRIs. We therefore produce three grand overview tables (similar to evidence map) mapping the amount of data available according to PICO criteria (please see Table 1-3 in the report). The empty areas represent the areas need future research. We also made several suggestions for future DRI committees. Given the nature of this special evidence report, I would also consider this section as "Future Research" section in a typical evidence report. If you would accept above arguments, I would suggest change some information you extracted as follows (highlighted in yellow): - Were research gaps defined? yes - Was there an explicit framework/set of organizing principles (e.g. , PICO, a diagram) used for the identification of research gaps/needs? Yes (Table 1-3)	This report was not a typical evidence report. Please see more details in previous question.

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8 (cont.)	Tufts University EPC (cont.)	Vitamin D and calcium: A systematic review of health outcomes[13] (cont.)		- Were future research gaps/ needs provided, and where were they found? Yes, Table 1-3 and in the last section of Chapter 4. How were research gaps/needs presented? Tables and texts.	
9	University of Alberta EPC	Diabetes education for children with type 1 diabetes mellitus and their families[14]	No	The summary accurately reflects our approach and presentation.	We don't have a process in place regarding the research/gaps needs section.
10	University of Minnesota EPC	Integration of mental health/substance abuse and primary care[15]	We used the discovery process that is inherent in the review process. If a question is difficult to answer with the given literature, it becomes apparent. Since there is generally always more research that can be done, we generally try to keep to the research gaps that are more pressing, rather than be exhaustive. It is also not uncommon to have research gaps arise during conversations with TEP members. These are also usually noted and incorporated into the discussion section.	The organizing framework was the key questions themselves.	We have not implemented a different process. There has not yet been the need.

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11	University of Ottawa EPC	Diagnosis and treatment of erectile dysfunction[16]	We used implicit (not explicit) framework to identify research gaps across PICO which was based on the analytic framework (page 18 of the report). The guiding principle was the degree to which a given research question was addressed by the identified evidence. This degree depended on an informal summary of constituent elements of strength of the reviewed evidence such as individual study quality, presence/absence of evidence, amount of evidence, consistency of results, or clinical relevance of outcome measures.	See answer to previous question.	Although we now started using the formal grading system of evidence proposed by AHRQ to rate overall strength of evidence, we have not yet utilized an explicit framework for defining and identifying research gaps.
12	Vanderbilt University EPC	Treatment of overactive bladder in women[17]	Yes, although we would note that the terms "research gaps" and "research needs" had not entered the EPC language at the point this report was prepared and submitted for peer review. Overall our team has gravitated toward topics in which there are known and concerning gaps in the literature (e.g., management of uterine fibroids; fetal surgery), limitations in the study design and measurement methods of prior research (e.g., overactive bladder; definitions of chronic pelvic pain, fibroids in pregnancy), reservations about the quality of the technical implementation or documentation of research (e.g., new technologies for cervical cancer screening;	No, we consider most of our process internal ground work that helps assure a standardized process so that we don't overlook any domains. Given desire for brief and readily consumed reports, we don't find advantage to introducing more materials about method/process in the reports themselves (especially now with the development of future research needs documents as a separate product), but we would welcome some documentation of acceptable approaches that we could cite in order to refer interested readers to more detail and to be able to more briefly summarizes the approach used. INFORMATION INCLUDED IN THE ABSTRACTION TABLE - Were research gaps defined? One described approach was to consider deficits that kept studies from achieving "good" quality ratings	We are still using the same core method, sometimes with embellishments where the gaps are more unique to the topic for instance a surgical device, diagnostic approach, or rare but devastating outcome. We are also currently leading a pilot project to explore ways of preparing the separate documents that will be focused on research gaps/needs. That project emphasizes using electronic processes to snow-ball ideas about gaps/needs and to then rank which have greatest attractiveness/urgency from the perspective of stakeholders.

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12 (cont.)	Vanderbilt University EPC (cont.)	Treatment of overactive bladder in women[17] (cont.)	secondary wound closure), a dearth of direct comparisons of treatments (e.g., management of preterm labor, episiotomy approach), modest use of patient reported outcome measures (cesarean on maternal request), little information about modifiers of treatment outcomes (traumatic brain injury), and a small pool of studies with direct applicability to the diversity of the clinical populations in which the diagnostic tool, device, or treatment is deployed (virtually universal). With few exceptions our work has included substantial components of non-randomized trial evidence so these challenges exist for all the reviews and are common dilemmas to be confronted in future research. From this experience we have developed a detailed framework for identifying research needs. We routinely consider the following information to characterize the status of current research and the needs for future research: • Inventory and appraisal of strengths and weaknesses of operational definitions used at each phase of the research: inclusion and exclusion, exposures, outcomes, and key covariates/modifiers.	(p. 105). However, we concur we didn't define what we meant by "gaps" -it wasn't EPC jargon at the time the final draft was submitted – long lag to publication. - Was there an explicit framework/ set of organizing principles (e.g. , PICO, a diagram) used for the identification of research gaps/needs? Same comments – don't think we were focused on the concept of gaps/needs in the way we are now at the time the report was prepared. Agree not methods described. - Were future research gaps/ needs provided, and where were they found? Because gaps/needs is somewhat vague, I'd encourage us to keep thinking about specific needs for improvement in research methods that apply to the field as its own content.	Would like to go on using a similar approach but time/effort/cost constraints will likely make this infeasible for the CERs themselves. Suspect these methods will be reserved to the future research needs documents when they are done as separate reports.Separate from EPC work we are exploring machine learning methods to glean future research needs from other documents more efficiently to explore whether this can be done more systematically.

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12 (cont.)	Vanderbilt University EPC (cont.)	Treatment of overactive bladder in women[17] (cont.)	• Documentation of measurement methods used to implement operational definitions, with details such as documentation of validation and reliability of measures, for example commenting on the implications of defining gestational age at birth based on last menstrual period, birth certificate data, or ultrasound; or determining presence of a condition by medical record review, ICD-9, patient interview, or adjudicated decision trees. • Semi-quantitative inventory of the prior study designs and the evidence or lack of evidence of the natural progression from lower levels of evidence through higher levels of evidence over time. • Explicit documentation of gaps in availability of direct comparisons in comparable groups of common clinical care or diagnostic approaches. • Applicability of existing research to the spectrum of individuals encountered in typical clinical practice and the possible influences of study design on understanding the likely achieved effects in real-world settings.		

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12 (cont.)	Vanderbilt University EPC (cont.)	Treatment of overactive bladder in women[17] (cont.)	• Level of clinical uncertainty acknowledged by experts, providers, stakeholder organizations, and individuals. • Degree to which the research provides insights into modifiers of treatment response, test performance characteristics, or device-related complications. (Generally we have key question focused on knowledge about modifiers. Given scant attention in most literature, this key question becomes an opportunity to discuss why it is an important gap within the key question results and discussion.) • Ethical frameworks that inform understanding of prior research and feasibility and design of future research. • Potential influence of conflict of interest and regulatory requirements on the content of the literature and the nature of studies being conducted within a field. (See table 32 in OAB report for example of data to capture this.) Last as a working tool (not a component of the report) we consider a grid that includes the PICOTS elements along one axis in rows, and the elements outlined above along the other axis as column. This approach clearly identifies areas of concern as "vacancies" in the grid.		

EPC #	EPC Name	Title of Evidence Report (Ref No.)	Question: Did You Use a Specific Framework or Method To Identify Research Gaps? If so, Please Describe the Method Below.	Question: Do You Have Any Corrections or Clarifications on What Was Abstracted? If so, Please List Them Below.	Question: Have You Implemented a Different Process Since Publishing the Above-Mentioned Report? If so, Please Provide a Description of the Process, and Indicate When it Was Implemented.
12 (cont.)	Vanderbilt University EPC (cont.)	Treatment of overactive bladder in women[17] (cont.)	Team members and an information scientist as well as the TEP are also involved in creating an inventory of ongoing trials/other important studies. We weigh this information (and often present it) in deciding what to emphasize or to tell readers to be looking for in future literature that may help close gaps. Within the EPC and the project teams we then discuss and ultimately establish consensus about the relative level of importance of particular elements to emphasize in the future research materials for a specific review. Of note, though at times encouraged to do so, we rarely describe specific studies that should be prioritized preferring to highlight methods that will provide cross-cutting improvements in the research, and a longer listing of gaps/needs without a sense of which is most important because different funders and research communities will likely have differential ability to focus on gaps/needs.		

Abbreviations: AHRQ=Agency for Healthcare Research and Quality, ARRA=American Recovery and Reinvestment Act, CER=comparative effectiveness review, DRI=dietary reference intake, HER2=human epidermal growth factor receptor 2, ICD=international classification of diseases, IOM=Institute of Medicine, IT=information technology, PICO=population, intervention, comparison, and outcomes, PICOS=population, intervention, comparison, outcomes, and settings, RAND=research and development, RCT=randomized controlled trial, RTI=Research Triangle Institute, TEP=technical expert panel, UNC=university of North Carolina.

Appendix D. Step 3: Review of Current Practices of Organizations Involved With Evidence Synthesis—List of Contacted Organizations

Sr No.	Country	Organization	Acronym	Activities
1	Argentina	Institute for Clinical Effectiveness and Health Policy	IECS	HTA
2	Australia	Adelaide Health Technology Assessment	AHTA	HTA
3	Australia	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	ASERNIP-S	HTA
4	Australia	Medical Services Advisory Committee	MSAC	HTA
5	Australia	Caring for Australasians with Renal Impairment	CARI	systematic reviews
6	Australia	Joanna Briggs Institute	JBI	systematic reviews
7	Australia	National Breast and Ovarian Cancer Centre	NBOCC	systematic reviews
8	Australia	Centre for Clinical Effectiveness	CCE	systematic reviews, HTA
9	Austria	Gesundheit Österreich GmbH	GÖG	HTA
10	Austria	Ludwig Boltzmann Institut für Health Technology Assessment	LBI of HTA	HTA
11	Belgium	Belgian Health Care Knowledge Centre	KCE	HTA
12	Brazil	Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	DECIT-CGATS	HTA
13	Canada	Agence d'évaluation des technologies et des modes d'intervention en santé (Québec Government Agency responsible for Health Services and Technology Assessment)	AETMIS	systematic reviews, HTA, CEA
14	Canada	Canadian Agency for Drugs and Technologies in Health	CADTH	HTA
15	Canada	Institute of Health Economics	IHE	HTA
16	Canada	Medical Advisory Secretariat	MAS	HTA
17	Canada	Program in Evidence-based Care	PEBC	systematic reviews
18	Chile	Department of Quality and Patient Safety of the Ministry Health of Chile	ETESA	HTA
19	Denmark	Danish Centre for Evaluation and HTA	DACEHTA	HTA
20	Denmark	Danish Institute for Health Services Research	DSI	HTA
21	Finland	Finnish Office for Health Technology Assessment	FinOHTA	HTA
22	France	Comité d´Evaluation et de Diffusion des Innovations Technologiques	CEDIT	HTA
23	France	Haute Autorité de Santé	HAS	HTA
24	Germany	German Agency for HTA at the German Institute for Medical Documentation and Information	DAHTA@DIMDI	HTA
25	Germany	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	IQWiG	HTA
26	International	International Network of Agencies for Health Technology Assessment	INAHTA	HTA
27	Ireland	Health Information and Quality Authority	HIQA	HTA

Sr No.	Country	Organization	Acronym	Activities
28	Israel	Israel Center for Technology Assessment in Health Care	ICTAHC	HTA
29	Italy	HTA Unit in A. Gemelli Teaching Hospital	UVT	HTA
30	Italy	The Agency for Regional Healthcare	Age.na.s	HTA
31	Korea	Committee for New Health Technology Assessment	CNHTA	HTA
32	Lithuania	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	VASPVT	HTA
33	Malaysia	Health Technology Assessment Section, Ministry of Health Malaysia	MaHTAS	HTA
34	Mexico	Centro Nacional de Excelencia Tecnológica en Salud	CENETEC	HTA
35	New Zealand	Health Services Assessment Collaboration	HSAC	HTA
36	Norway	Norwegian Knowledge Centre for the Health Services	NOKC	HTA
37	Poland	Agency for Health Technology Assessment in Poland	AHTAPol	HTA
38	Spain	Agencia de Evaluación de Tecnologias Sanitarias	AETS	HTA
39	Spain	Andalusian Agency for Health Technology Assessment	AETSA	HTA
40	Spain	Basque Office for Health Technology Assessment	OSTEBA	HTA
41	Spain	Catalan Agency for Health Information, Assessment and Quality	CAHIAQ	HTA
42	Spain	Galician Agency for Health Technology Assessment	AVALIA-T	HTA
43	Spain	Unidad de Evaluación de Tecnologías Sanitarias	UETS	HTA
44	Sweden	The Swedish Council on Technology Assessment in Health Care	SBU	HTA
45	Switzerland	Medical Technology Unit - Swiss Federal Office of Public Health	MTU-SFOPH	HTA
46	Taiwan (China)	Center for Drug Evaluation	CDE	HTA
47	Thailand	Health Intervention and Technology Assessment Program	HITAP	HTA
48	The Netherlands	College voor Zorgverzekeringen	CVZ	HTA
49	The Netherlands	Gezondheidsraad	GR	HTA
50	The Netherlands	The Medical and Health Research Council of The Netherlands	ZonMw	HTA
51	UK	Centre for Reviews and Dissemination	CRD	systematic reviews, HTA, CEA
52	UK	NIHR Coordinating Centre for Health Technology Assessment	NETSCC, HTA	HTA
53	UK	National Horizon Scanning Centre	NHSC	HTA
54	UK	National Institute for Health and Clinical Excellence	NICE	systematic reviews, HTA, CEA
55	UK	Quality Improvement Scotland	QIS	HTA
56	UK	Royal College of Nursing	RCN	systematic reviews, CEA

Sr No.	Country	Organization	Acronym	Activities
57	UK	Scottish Intercollegiate Guidelines Network	SIGN	systematic reviews
58	US	American Academy of Otolaryngology - Head and Neck Surgery Foundation	AAO-HNS	systematic reviews
59	US	American College of Physicians	ACP	systematic reviews, HTA
60	US	American Society of Clinical Oncology	ASCO	systematic reviews
61	US	American Urological Association	AUA	systematic reviews, HTA
62	US	Center for International Rehabilitation	CIR	HTA
63	US	National Kidney Foundation	NKF	systematic reviews
64	US	VA Technology Assessment Program	VATAP	HTA

Abbreviations: CEA=cost-effectiveness analysis, GmBH=gesellschaft mit beschränkter haftung, HTA=health technology assessment, NIHR=National Institute for Health Research, UK=United Kingdom, US=United States, VA=veterans affairs.

Appendix E. Step 3: Review of Current Practices of Organizations Involved With Evidence Synthesis—Responses Obtained and Final Determinations of Formal Processes

Sr no.	Country	Organization	Acronym	Question: Do You Have a Formal Process for Identifying Research Gaps?	Question: When Was This Process Initiated?	Question: Please Provide a Description of the Formal Process.	Our Classification of Process
1	Argentina	Institute for Clinical Effectiveness and Health Policy	IECS	No	-	-	-
2	Australia	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical	ASERNIP-S	No	-	-	-
3	Australia	Medical Services Advisory Committee	MSAC	No	-	Comments: 1. MSAC does not have a formal process for research gap identification. 2. The closest that MSAC gets is to include comment on level of evidence in its assessment reports. 3. Where the gap is significant enough to impact on its ability to provide advice it may subsequently alert the MSAC secretariat which will inform the Department. 4. Neither MSAC nor the Department undertakes specific 'research' gap filling on a regular basis. 5. The closest that MSAC gets to this is to advise that interim funding be considered to allow data capture that could enhance a subsequent MSAC review of public funding. In many instances this is data capture such as utilization numbers and trends managed in the department - not necessarily “research.” 6. Researchers have independently used MSAC reports and MSAC Public Summary Documents (that provide the rationale for its advice) in order to support	-

Sr no.	Country	Organization	Acronym	Question: Do You Have a Formal Process for Identifying Research Gaps?	Question: When Was This Process Initiated?	Question: Please Provide a Description of the Formal Process.	Our Classification of Process
3	Australia (cont.)	Medical Services Advisory Committee (cont.)	MSAC	No	-	applications to research agencies for research funding. 7. Horizon scanning of new or upcoming technologies is also carried out but through the auspices of AHMAC please see www.horizonscanning.gov.au, In doing this research gaps may again be identified.	-
4	Australia	Caring for Australasians with Renal Impairment	CARI	Yes	1999-2000	1. Guideline writers are asked to write suggestions for future research when they draft their guidelines. A list of these suggestions is sent to the Australian Kidney Trials Network which is responsible for deciding which research gaps have priority and should be included in their work program. 2. When a new guideline topic is suggested/ needed we perform a literature search and review the results. The steering committee (13 members) assesses which topics have most need of being addressed and match these with lit searches that yield good evidence.	Not formal
5	Australia	Centre for Clinical Effectiveness	CCE	No	-	-	-

Sr no.	Country	Organization	Acronym	Question: Do You Have a Formal Process for Identifying Research Gaps?	Question: When Was This Process Initiated?	Question: Please Provide a Description of the Formal Process.	Our Classification of Process
6	Australia	Joanna Briggs Institute	JBI	Yes	1996	The Institute undertakes systematic reviews, both centrally in Adelaide, and through its international collaboration of 65 centers located on every continent. These reviews are published and loaded in an online library for access. As systematic reviews examine the published literature related to a particular intervention or outcome, reviews are also able to identify strengths and weaknesses as well as knowledge gaps in the underlying primary research base. In conducting systematic reviews, the Institute uses a standardized approach based on methodological criteria for quality, transparency and methodological rigor. For each review published, this includes a detailed analysis and commentary on the gaps in the primary research that were identified during the conduct of the systematic review. Each review undertaking through the collaboration is required to include a section that describes specific gaps in the research literature and provide some commentary on these gaps and how they might be addressed. When published, these are available to primary researchers and organizations internationally. The institute also publishes a monograph series that includes reports that specifically focus on the gaps identified by systematic reviews. This is an occasional series as our primary approach is via the relevant sections of the systematic review report.	Not formal
7	Austria	Gesundheit Österreich GmbH	GÖG	No	-	-	-

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8	Austria	Ludwig Boltzmann Institut für Health Technology Assessment	LBI of HTA	No	-	-	-
9	Canada	Agence d'évaluation des technologies et des modes d'intervention en santé (Québec Government Agency responsible for Health Services and Technology Assessment)	AETMIS	No	-	Comments: Our organization does not have any formal process for identifying research gaps. In our HTA reports we do often identify research gaps, but there is no formal process in place.	-
10	Canada	Canadian Agency for Drugs and Technologies in Health	CADTH	Yes	Not yet	Please note that our organization is currently undergoing an internal reorganization, bringing together what used to be 3 distinct HTA-like programs. Over the course of the next year, we will be "harmonizing" our processes – with the likely end goal that the process for identifying research gaps/needs that existed in one of these programs (the COMPUS program) will be applied across the organization. The link to CADTH's COMPUS process is as follows: http://www.cadth.ca/index.php/en/compus/process/summaryThe output of the gaps and key messages" component of the process is a document that provides a "gap analysis;" this report is published on our website, may be published in peer-reviewed journals and (as of right now) shared in a more informal manner with our national health services research funding body, CIHR.Also note that Canada now has the "Drug Safety & Effectiveness Network" (DSEN) that is funded by Health Canada, and located at the Canadian Institutes for Health Research (CIHR). This network is in its infancy, so the mechanisms by which research gaps/needs are identified & addressed are	Not formal

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10	Canada (cont.)	Canadian Agency for Drugs and Technologies in Health (cont.)	CADTH	Yes	Not yet	still being elucidated. It is also important to note that this network considers only drugs/pharmaceuticals; the other facets of health care are not covered. For more information on DSEN, please see: http://www.cihr.ca/e/40269.html	Not formal
11	Canada	Institute of Health Economics	IHE	No	-	Comments: "Published and article, "Using HTA to Identify Research Gaps: A Pilot Study", in 'Health Policy' in 2008 based on this work."	-
12	Canada	Medical Advisory Secretariat	MAS	No	-	Comments: Our HTA process is application driven, or through requests from the Minister of Health office.	-

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13	Canada	Program in Evidence-based Care	PEBC	Yes	1995	PEBC is a guideline development organization located within the academic environment of McMaster University and funded by the Ontario Ministry of Health through Cancer Care Ontario. From the inception of the program in 1995, topics for guideline development have been put forward by our clinical partners who are practicing clinicians in the cancer care delivery system in Ontario. The impetus to begin a new PEBC guideline project may come from an existing Disease Site Group/Guideline Development Group (DSG/GDG), CCO Clinical Programs or Executive Team, the Ontario Ministry of Health and Long Term Care or other stakeholders in the Ontario cancer system. Some common criteria used to set priorities include the burden of disease, emergence of new care options, unwanted variation in clinical practice, opportunity to improve quality of care, safety or system performance, and new evidence.	Formal process for setting priorities for guideline development. Organizing Principle: None identified

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14	Finland	Finnish Office for Health Technology Assessment	FinOHTA	Yes	Jan-10	We have three separate pathways1. Rapid reviews, which we are doing in co-operation with Finnish hospital districts (n=20). The representatives of the hospital districts form a committee, which is supposed to feed FinOHTA with information needs. We get suggestions for new evaluation technology with a mini-HTA questionnaire (attached). Finohta's MUMM (Managed Uptake of Medical Methods) group scopes the suggested technology and the committee chooses 5-10 technologies to be evaluated per year.When review is finished, the information gaps are identified separately and listed in the conclusion of the report. Reports are available in Finnish only (Summaries in English).2. Screening program. The secretariat for the Screening Committee of the Ministry of Health is in FinOHTA, and FinOHTA is supposed to asses all screening programs the Committee requires. Secretariat prepares a full HTA and gives a detailed presentation with experts for the screening group before the decision to evaluate the program is made. Research gaps are identified separately and presented. The Committee may decide that before a screening program is launched nationally, the missing information shall be collected through a pilot program. For example, currently a pilot study on screening colorectal cancer is collecting data about willingness to participate, effectiveness, and feasibility of organizing the screening in different	Not formal

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14	Finland (cont.)	Finnish Office for Health Technology Assessment (cont.)	FinOHTA	Yes	Jan-10	areas.[3]. FinOHTA also prepares full HTA reports. Anybody can suggest a topic for evaluation. FinOHTA scopes the topic and decision to make a full HTA is made by our scientific committee of external experts. The decision is based on a structured evaluation of relevance. The decision to make a report is not dependent on information about evidence gaps. If gaps are identified during the HTA process, they are presented as part of the formal summary of the document.	Not formal
15	France	Haute Autorité de Santé	HAS	No	-	Comments Our organization may indeed identify evidence gaps when assessing health technologies and may recommend additional evidence generation. Following our recommendations, additional trials, studies or registries can be required by decision makers. These requirements may either be included in the agreement with manufacturers during pricing negotiations or be included within a conditional reimbursement framework. Additional studies may be required for all types of technologies. Nevertheless, we don't have a formal process for identifying research gaps/needs.	-
16	Germany	German Agency for HTA at the German Institute for Medical Documentation and Information	DAHTA@DIMDI	No	-	-	-
17	Israel	Israel Center for Technology Assessment in Health Care	ICTAHC	No	-	-	-

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18	Italy	HTA Unit in A. Gemelli Teaching Hospital	UVT	Yes	September, 2006	(NOTE: This date is referred to the "gap assessment procedure" start, the procedure of overcoming the evidence gap is still informal)Unità di Valutazione delle technology (UVT -HTA Unit) active at "A. Gemelli" University Hospital has been involved in HTA at Meso levels for about ten years, to support decisions making process regarding the introduction into clinical practices of new health technologies. According to a formal procedure, the staff of UVT advise the hospitals management in difficult resource allocation decisions, using an approach based on scientific technology assessments through the formulation of recommendation. The procedure starts from a request of a new medical technology (innovative, high cost and not yet used into hospital clinical practice) by a clinical department. The results of evaluation activity are assessment reports in which are considered all the relevant topics for an hospital context (decryption of the technology, regulatory status, systematic review of the evidence, alternatives and economics' issues). In the figure 1 are reported the phases of the assessment procedure, particularly UVT manages directly the IInd, IIIrd, IVth phases. Frequently, because of the evaluated technologies are really innovative we point out a scarcity of evidence on which basis to formulate a recommendation. When we observed the lack of evidence we plan a meeting with referral clinicians, pharmacy unit,	Not formal

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18	Italy (cont.)	HTA Unit in A. Gemelli Teaching Hospital (cont.)	UVT	Yes	September, 2006	administrative unit in order to evaluate the possibility to elaborate an observational protocol for testing the new medical technology and to implement a phase of practice trial. During the meeting with clinician we define the specific clinical end points to investigate in the real hospital's context treating real patients. Those end points are specified in a procedure of testing (the test isn't a very clinical study) in which are established also the temporal range of observation. Instead during the meeting with pharmacy and administrative offices we consider the modality of introduction of restricted use of technology (e.g., for payments topic for free or limited in number).	Not formal
19	Lithuania	State Health Care Accreditation Agency under the Ministry of Health of the Republic of Lithuania	VASPVT	No	-	-	-
20	Malaysia	Health Technology Assessment Section, Ministry of Health Malaysia	MaHTAS	No	-	-	-

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21	Mexico	Centro Nacional de Excelencia Tecnológica en Salud	CENETEC	No	-	Comments: From February 2006 a project to gradually building a priority-setting methodology for complex diseases to be eventually covered by the resources Catastrophic Expenses Fund was developed by the Mexican Ministry of Health towards the General Health Council. The most recent version of the methodology started operations in February 2008. CENETEC participates in working groups in developing a studies and discussions to evaluate clinical, economic, ethical and social acceptability criteria inherent to the set of complex diseases identified as candidates for gradual coverage. Quantitative and qualitative methods are used during the evaluation. As an HTA agency, we seek to inform decisionmaking by examining the effects of a particular technology with respect to its safety and effectiveness as well as its social, economic and ethical implications that allow to prioritize interventions that would help to achieve the Health Goals in the country.	-

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22	New Zealand	Health Services Assessment Collaboration	HSAC	Yes	2007	Health Services Assessment Collaboration (HSAC, in association with Health Technology Associates, Sydney) conducts health technology assessments and systematic reviews as a way to determine effectiveness of health care interventions and services. The context of these appraisals are framed by the target population, the intervention or set of interventions under consideration, the comparator (either usual care process, or another alternative technology, or a specified population group based on the research question), and the defined measurable health outcomes. For HSAC, identification of the research gaps is a two-step process. In the first step, the research needs are identified by health care professionals throughout New Zealand and are submitted to the Ministry of Health. HSAC discusses these proposals with the officials in a prioritization meeting in order to decide the relative importance and rank order the relevance and applicability of these proposals. Once the proposals are finalized for review and further research, HSAC researchers initiate the step two for identifying the specific research gaps within the “accepted” proposals. This is done through the process of initially developing a “scoping protocol” for each research project by defining the research question, and identifying the population, intervention, comparator, and outcomes for each research project for defining the research need. During this process, the	Formal process for setting priorities for systematic reviews and HTAs Organizing Principle: PICO

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22	New Zealand (cont.)	Health Services Assessment Collaboration (cont.)	HSAC	Yes	2007	scoping protocols are referred back to the clients (those who requested the specific reviews or health technology assessments in the first place) . This is a consensus driven iterative process. Once the research gaps are thus identified, and the question for the review is finalized, the review process ensues.	Formal process for setting priorities for systematic reviews and HTAsOrganizing Principle: PICO
23	Spain	Agencia de Evaluación de Tecnologias Sanitarias	AETS	No	-	-	-
24	Spain	Catalan Agency for Health Information, Assessment and Quality	CAHIAQ	Yes	1996	The Catalan Agency for Health Information, Assessment and Quality (CAHIAQ), formerly the Catalan Agency of Health Technology Assessment and Research (CAHTA), efforts to identify knowledge gaps are addressed to priority setting for research/assessment of health services, the identification of effective interventions and the field of applied translational research. In particular, CAHIAQ has been ruling every two-years a Call for Topics among the regional decision-making and scientific community, which subsequently are submitted to a Priority-setting process to identify a number of prioritized topics for which the CAHIAQ Research Call on applied health research is subsequently launched. This process is being done to be accountable with CAHIAQ mission to identify knowledge gaps provide scientifically-based information to regional healthcare decision makers.	Formal process for identifying primary research gaps/needs. Organizing Principle: None identified

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25	Sweden	The Swedish Council on Technology Assessment in Health Care	SBU	Yes	November, 2009	We have just started a project on identifying knowledge gaps. The project is a mandate from the Ministry of Social Affairs. Our aim is to delineate uncertainties that cannot be answered with reference to reliable and up-to-date systematic reviews explicit and actively disseminate knowledge about which treatments that are not sufficiently evaluated. We have formed a steering group with representatives from various stakeholders who can give us input into the work. Our first task is to build a database of uncertainties.	Not formal
26	Switzerland	Medical Technology Unit - Swiss Federal Office of Public Health	MTU-SFOPH	No	-	-	-
27	Taiwan (China)	Center for Drug Evaluation	CDE	No	-	-	-

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28	The Netherlands	The Medical and Health Research Council of The Netherlands	ZonMw	Yes	1998	Government ministries, the Netherlands Organization for Scientific Research and other organizations commission ZonMw to find solutions to certain problems or to boost work in particular areas. Together with experts from the field, ZonMw analyses the current state of play, the problems that exist, the priorities and where to look for solutions. We then incorporate our findings into a program – a plan of action that sets out the direction for developments in scientific research and health care. The programme gives scientific and health care institutions the opportunity to conduct research or to develop, test and implement innovations on a project basis. ZonMw's main commissioning bodies are the Ministry of Health, Welfare and Sport and Netherlands Organization for Scientific Research .In other words, identification of research gaps is a constant part of our program development strategy. Process and methods used depend on the topic and area, and could include literature review, field research, expert / focus group and other kinds of meetings, interviews. In some cases extensive scientific research is being commissioned.	Not formal

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29	UK	NIHR Coordinating Centre for Health Technology Assessment	NETSCC, HTA	Yes	1993	Since the HTA programme commenced funding in 1993, identification and prioritization has formed a major aspect of the commissioning workstream. As the programme has expanded, the need for greater expansion in the identification of topics has arisen and a formalized identification team started in 2005. Similarly, as NETSCC now manages 5 programmes, there is a need to feed topics across all 5 research programmes. Topics are suggested via a web-based form, via panel members, panel researchers and through working with external agencies. These topics are all checked by the consultant advisors for their remit including whether there is an NHS need and also go through a series of panels (with clinicians, academics present) to decide relevance to the NHS. Since our restructure earlier this year, we have a newly formed Identification Team that is working towards establishing a NETSCC wide strategy for identification of topics.	Not formal
30	UK	National Horizon Scanning Centre	NHSC	No	-	-	-

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31	UK	National Institute for Health and Clinical Excellence	NICE	Yes	Unknown	9.5 Formulating research recommendations The GDG is likely to identify areas in which there are uncertainties or where robust evidence is lacking. This section provides a framework for highlighting these uncertainties and translating them into research recommendations. Advice is also given about identifying “high-priority” research recommendations for inclusion in the NICE version of the guideline. Research recommendations can cover questions about any aspect of the guidance and are designed to address uncertainties that have been identified. Examples include clinical or cost effectiveness, implementation, outcomes, equality issues, the accuracy of a test, diagnosis, prognosis, rates of harm or other events, patients’ experience, measurements of outcome, and service delivery and organization. Primary research or secondary research (for example, systematic reviews) can be recommended. 9.5.1 Principles for formulating research recommendations Research recommendations should be formulated as questions. A section that includes the questions requiring further research should be included as an appendix to the full guideline. These research questions may also be highlighted in individual chapters. Each research question should relate to an uncertainty or evidence gap that has been identified during the guideline	Formal process for identifying primary research gaps/needs as well as setting priorities for systematic reviews. Organizing Principle: PICO

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31	UK (cont.)	National Institute for Health and Clinical Excellence (cont.)	NICE	Yes	Unknown	development process. Each research recommendation should be formulated as an answerable question or a set of closely related questions. This should use the PICO (patient, intervention, comparison and outcome) framework. 9.5.2 Selecting high-priority research recommendations for the NICE guideline To help ensure that research addresses key areas, for a standard clinical guideline the GDG should select up to five high-priority research recommendations to include in the NICE version of the clinical guideline. These should be identified using the criteria in table 9.2. Each high-priority research recommendation should be summarized in a single paragraph (ideally no longer than 150 words) that describes why the proposed research is important (for an example, see box 9.5). The reasons for selecting each high-priority research recommendation should be presented in a table in an appendix to the full guideline, using table 9.2 as a template, and indicating if any information is unavailable. The high-priority research recommendations for each clinical guideline will be posted on the NICE website[3]. They will then go through a second prioritization process within NICE that considers all research recommendations relating to all types of guidance produced by NICE.	Formal process for identifying primary research gaps/needs as well as setting priorities for systematic reviews. Organizing Principle: PICO

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32	UK	Royal College of Nursing	RCN	No	-	Comment:Whilst we do not have a current organization-wide system for identifying research priorities we have undertaken a number of processes over the years to identify gaps in professional nursing knowledge / nursing research priorities. These can be found here http://www.rcn.org.uk/development/researchanddevelopment/policy/prioritiesIn addition we are in the process of implementing a new organization wide research strategy and as a consequence of recommendation no 6, we are revising our research governance and management arrangements. This will enable us to develop an implement an organization wide research priority setting process. Your survey is therefore timely and I look forward to reading your final report. With best wishes.	-

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33	UK	Scottish Intercollegiate Guidelines Network	SIGN	Yes	Unknown	Guideline Development Groups (GDGs) establish a set of key questions to form the basis of a guideline. Evidence is gathered and reviewed for each of these questions. If a question is seen as particularly important and there is no evidence, or only such poor evidence that the GDG does not feel able to make a recommendation, then a recommendation for further research will be made. These recommendations are included in published guidelines. Research grants in the National Health Service in Scotland are made by the Chief Scientists Office, who has a formal process for rating grant applications. A grant proposal specifically linked to a recommendation for research in a SIGN guideline will get additional points in the scoring system. We are also planning to contribute to the DUETS database (http://www.library.nhs.uk/duets/) which is intended as a source of research topics in health care for across the UK.	Formal process for identifying primary research gaps/needs. Organizing Principle: Key question

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34	US	American Academy of Otolaryngology - Head and Neck Surgery Foundation	AAO-HNS	Yes	Unknown	The American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) Foundation identifies research gaps/needs through a variety of avenues including clinical practice guidelines, AAO-HNS Research Advisory Board (RAB), and the Centralized Otolaryngology Research Efforts (CORE) Grant Program. 1. Clinical practice guidelines developed at the AAO-HNS are based on systematic literature reviews on a particular topic. A "Research Needs" section is developed by the guideline panel that identifies gaps and needs after evaluation of the literature. 2. The AAO-HNS RAB consists of 12 officers, including both AAO-HNS members and nonmember stakeholders active in otolaryngology research. The RAB provides a voice for otolaryngology research needs and partnership opportunities of the community at large. 3. In an effort to strengthen research support in all areas of otolaryngology, the AAO-HNS Foundation has joined forces with several senior societies, foundations and sponsors to broaden research opportunities, and to streamline and enhance the research application and review process. CORE serves as a central clearinghouse and facilitator for otolaryngology-head and neck surgery research programs. The research funded by CORE may lead to further identification of research needs.	Not formal

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35	US	Center for International Rehabilitation	CIR	No	-	-	-
36	US	National Kidney Foundation	NKF	Yes	1997	In each of our guideline development projects, we identify the development of research recommendations as a goal. Workgroup members are asked to formulate recommendation for future research towards the end of the guideline development process based on what kind of research would help fill evidence gaps that were encountered in the systematic reviews conducted for the guidelines and in the formulation of the recommendations. Criteria for recommending future research are that this research should either address a question that would directly inform and area of clinical practice that is currently unaddressed or a question that would make the evidence base underpinning a weak recommendation more definitive. The workgroup members are prompted to use the PICOD format for defining populations, interventions (or predictors), comparators, outcomes and time points for outcome measurement. The workgroup is also asked to prioritize the research recommendations across the topics in the guideline. Describe how the research recommendations in the guidelines are then used for the RFAs for KDOQI research grants as competitions in a research initiative designed to stimulate investigation addressing the research recommendations that accompany the Kidney Disease Outcomes Quality	Formal process for identifying primary research gaps/needs. Organizing Principle: PICOD

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36	US	National Kidney Foundation (cont.)	NKF (cont.)	Yes	1997	Initiative (KDOQI) guidelines. The topics for this Request for Application (RFA) were selected by the KDOQI Research Advisory Committee based upon the following criteria: • Areas that are ripe for study, i.e., where there is a gap in knowledge but there is some preliminary evidence suggesting that research could be fruitful; • Impact on patient outcomes; • Likelihood that meaningful progress on the research topic could be generated at the level of NKF support; • Interest of policymakers (Congress, CMS, FDA); • Likelihood that investigator may be able to secure funding (from NIH or industry) to complete the study, or take the next steps towards improving patient outcomes. Answering the research recommendation questions will enable KDOQI to provide more authoritative guidance regarding appropriate tests and therapies in the future, lead to enhanced patient outcomes, advance patient advocacy and, ultimately, validate, critique, and improve guidelines. As a result, this research program should also contribute to the effective utilization of KDOQI guidelines and clinical practice recommendations.	Formal process for identifying primary research gaps/needs. Organizing Principle: PICOD

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37	US	VA Technology Assessment Program	VATAP	No	-	-	-

Abbreviations: AHMAC=Australian Health Ministers Advisory Council, CMS=Center for Medicare and Medicaid Services, CCO=Cancer Care Ontario, COMPUS=Canadian optimal medication prescribing & utilization service, CORE=centralized otolaryngology research efforts, DSEN=drug safety & effectiveness network, DUETS=database of uncertainties about the effects of treatments, FDA=Food and Drug Administration, GDG=guideline development group, GmBH=gesellschaft mit beschränkter haftung, HTA=health technology assessment, KDOQI=kidney disease outcomes quality initiative, MUMM=managed uptake of medical methods, NIH=National Institutes of Health, NIHR=National Institute for Health Research, PICO=population, intervention, comparison, and outcomes, RAB=research advisory board, RFA=request for applications, UK=United Kingdom, US=United States, VA=veterans affairs.

Appendix F. Step 4: Development of Framework—Instructions for Research Gaps Abstraction Worksheet

A research gap is a topic or area for which missing or inadequate information limits the ability of reviewers to reach a conclusion on a given question. This worksheet is designed to facilitate the identification and organization of research gaps during evidence reviews sponsored by AHRQ. Our aim was to design a simple, user-friendly worksheet to help investigators record research gaps. We envision that investigators would fill out this worksheet soon after the data synthesis phase, while in the process of writing the results section of the evidence report.

To facilitate the aggregation of research gaps identified by different people, each person should put his/her name/initials and date of completion on the top right corner of the sheet. Each person should also write the worksheet page number and the key question number on the top right corner of the sheet. We encourage members to be consistent in how they choose to fill out this worksheet, both within themselves as well as with other members of the investigative team.

In the worksheet table, each row is one research gap and is numbered accordingly ("Serial Number").

Reason(s) for Gaps

This column allows members to indicate why the research gap exists. The classification of the reasons for gaps are listed and coded in the legend of the gaps abstraction worksheet. Members should choose the most important reason(s) for the existence of the research gap. That reason selected should be the reason(s) that most precludes conclusions from being made. Put another way, members should consider what would be needed to allow for conclusions to be made. Members may choose to enter codes for more than one reason in this column, as appropriate. The specific reasons for gaps are listed in the footnote of the table and described below:

- Insufficient or imprecise information. Insufficient information in identified studies can arise if no studies are identified, if a limited number of studies are identified, or if the sample sizes in the available studies are too small to allow conclusions. If the information available in identified studies is insufficient to allow a conclusion or if the estimate of the effect (usually achieved from a meta-analysis) is imprecise there is a research gap. Correspondence to grading systems:
  - *EPC SOE:* **Precision** is a required domain.
  - *GRADE*: The GRADE Working Group advises decreasing the grade of the quality of the evidence if the data are "**imprecise** or sparse".
  - *USPSTF:* The following questions are considered while grading the evidence:
    - "How many studies have been conducted that address the key question(s)?"
    - "How large are the studies? (i.e., what is the precision of the evidence?)"
- Biased information. The aggregate risk of bias is contingent upon the risk of bias of the individual studies. In addition to considering methodological limitations of studies, the appropriateness of the study design should also be considered. Correspondence to grading systems:
  - *EPC SOE:* **Risk of bias** is a required domain. It incorporates the elements of **study design** and **aggregate quality** of the studies under consideration.
  - *GRADE:* **Study quality** and **study design** are key elements.
  - *USPSTF:* The following questions are considered while grading the evidence:

    - "To what extent are the existing studies of high quality? (i.e., what is the internal validity?)"
    - "Do the studies have the appropriate research design to answer the key question(s)?"
- Inconsistency or unknown consistency. Consistency is the degree to which reported effect sizes from included studies appear to go in the same direction. The two elements are whether effect sizes have the same sign (same side of "no effect") and whether the range of effect sizes is narrow. However, it should be kept in mind that a statistically significant effect size in one study and an effect size whose confidence interval overlaps null in another study do not necessarily constitute inconsistent results. If there is only one available study, even if considered large sample size, the consistency of results is unknown. Correspondence to grading systems:
    - *EPC SOE:* **Consistency** is a required domain.
    - *GRADE:* **Consistency** is a key element.
    - *USPSTF:* The following question is considered while grading the evidence:
        - "How consistent are the results of the studies?"
- Not the right information. There are a number of reasons why identified studies might not provide the right information. First, results from studies might not be applicable to the population and/or setting of interest. Second, the optimal or most important outcomes might not be assessed. Third, the study duration might be too short and patients might not be followed up for long enough duration to adequately assess some outcomes which might be most important. Correspondence to grading systems:
    - *EPC SOE:* **Directness** is a required domain. It also incorporates the element of surrogate versus clinical outcomes.
    - *GRADE:* **Directness** is a key element.
    - *USPSTF:* The following question is considered while grading the evidence:
        - "To what extent are the results of the studies generalizable to the general US primary care population and situation? (i.e., what is the external validity?)"

Characterization of Research Gaps

To further characterize the research gaps we propose using the PICOS framework using the population (P), intervention (I), comparison (C), outcomes (O), and setting (S). Those elements which are inadequately addressed in the evidence base should be characterized. The other relevant elements will be apparent from the key question from which the research is derived. It follows that for research questions that do not relate to a specific key question, all available elements of the research gap should be characterized.

Population (P)

In this column, team members should be as specific as possible about the age, sex, race/ethnicity, clinical stage, etc. of the population that is not adequately represented in the evidence base. However, it should be recognized that research gaps often do not relate to any specific population but refer to the general population.

Intervention (I)

In this column, team members should specify the name of the intervention that is inadequately included in the evidence base (generic names of drugs and devices are preferred), the duration of the

intervention, its dose, its frequency, who will administer it, etc. As with the population, it may not always be appropriate to specify great detail about the intervention.

Comparison (C)

In this column, team members should provide the same relevant details about the comparative intervention as for the intervention of interest – name of comparative intervention, its duration, its dose, its frequency, who will administer it, etc. If the comparison is "any other intervention," this should be indicated. Similarly, if the comparison is "no intervention" or placebo, it should be specified as such. It should also be recognized that there may be instances where there is no specific comparison of interest.

Outcomes (O)

In this column, team members should specify the relevant outcomes of interest that are inadequately included in the evidence base. It may be appropriate to organize outcomes by type of outcomes or to only list the types of outcomes (e.g., maternal outcomes and fetal outcomes, liver outcomes, and renal outcomes). If appropriate, the timing of outcome assessments that are missing should be specified. If there are no specific outcomes of interest, this should be indicated.

Setting (S)

In this column, when appropriate, team members should specify the relevant settings for research gaps.

Special Considerations

Research gaps relating to the accuracy of diagnostic tests can be fit into the PICOS framework by considering the diagnostic test under investigation as the intervention (I) and the gold standard test as the comparison (C). Relevant outcomes (O) in this case could include sensitivity and specificity.

Research gaps relating to the benefit of one form (or frequency) of clinical assessment (e.g., monitoring) versus another can be fit into the PICOS framework by considering these clinical assessments as intervention (I) and comparison (C). The comparison in this case could include a standard form (or frequency) of clinical assessment or no clinical assessment. Relevant outcomes (O) could include clinical outcomes to assess the benefit of the clinical assessment(s).

Research gaps relating to screening tests can be fit into the PICOS framework by considering these tests as intervention (I) and comparison (C). Relevant outcomes (O) could include clinical outcomes to assess the benefit of the screening test(s).

Research gaps which are difficult to characterize into the PICOS framework should be abstracted in free text form. Interventions could potentially include a range of treatment options, order of treatment options, individualization of treatments, etc. These are often gaps for which it is difficult to identify a clear intervention or comparison of interest.

Examples of research questions derived from such research gaps are: "What are the optimal glucose thresholds for medication use in women with gestational diabetes?"; "In what order should patients with cystic fibrosis perform their airway clearance therapies?" and "How should physicians choose an airway clearance therapy for a given patient with cystic fibrosis?"