Methods Guide
for Comparative Effectiveness Reviews

The Refinement of Topics for Systematic Reviews: Lessons and Recommendations From the Effective Health Care Program

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Comparative Effectiveness Reviews are systematic reviews of existing research on the effectiveness, comparative effectiveness, and harms of different health care interventions. They provide syntheses of relevant evidence to inform real-world health care decisions for patients, providers, and policymakers. Strong methodologic approaches to systematic review improve the transparency, consistency, and scientific rigor of these reports. Through a collaborative effort of the Effective Health Care (EHC) Program, the Agency for Healthcare Research and Quality (AHRQ), the EHC Program Scientific Resource Center, and the AHRQ Evidence-based Practice Centers have developed a Methods Guide for Effectiveness and Comparative Effectiveness Reviews. This Guide presents issues key to the development of Comparative Effectiveness Reviews and describes recommended approaches for addressing difficult, frequently encountered methodological issues.

The Methods Guide for Comparative Effectiveness Reviews is a living document, and will be updated as further empiric evidence develops and our understanding of better methods improves. Comments and suggestions on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews and the Effective Health Care Program can be made at www.effectivehealthcare.ahrq.gov.

This document was written with support from the Effective Health Care Program at AHRQ.

None of the authors has a financial interest in any of the products discussed in this document

Suggested citation: Buckley DI, Ansari M, Butler M, Williams C, Chang C. The Refinement of Topics for Systematic Reviews: Lessons and Recommendations From the Effective Health Care Program. Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. January 2013. AHRQ Publication No. 13-EHC023-EF. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

The Refinement of Topics for Systematic Reviews: Lessons and Recommendations From the Effective Health Care Program

Authors:

David I. Buckley, M.D., M.P.H.[a]

Mohammed Ansari, M.B.B.S., M.Med.Sc., M.Phil.[b]

Mary Butler, Ph.D.[c]

Clara Williams, M.P.A.[d]

Christine Chang, M.D., M.P.H.[e]

[a]Oregon Health & Science University Oregon EPC

[b]Ottawa Hospital Research Institute, CEP, Methods Center

[c]University of Minnesota, Minnesota EPC School of Public Health

[d]Kaiser Permanente Center for Health Research

[e]Agency for Healthcare Research and Quality

Acknowledgements

The authors gratefully acknowledge and thank the following individuals for their contributions to this project: Basmah Rahman, M.P.H., and Ngoc Wasson, M.P.H., for their administrative and project management support; Leah Williams, B.S., and Jeannine Ouellette for editing and formatting this paper; and associate editors Stephanie Chang, M.D., M.P.H., and Mark Helfand, M.D., M.P.H., M.S.

Peer Reviewers

Michelle Brasure, Ph.D.
Project Director, Minnesota
Evidence-Based Practice Center
Minneapolis, MN

Timothy S. Carey, M.D., M.P.H.
Co-Director, RTI-UNC Evidence-Based Practice Center
University of North Carolina at Chapel Hill
Chapel Hill, NC

Emma Irvin, B.A.
Director, Research Operations, Systematic Review Program
Institute on Work & Health
Toronto, ON, Canada

Joseph Lau, M.D.
Program Director, Tufts University Evidence-Based Practice Center
Tufts Medical Center
Boston, MA

Melissa McPheeters, Ph.D., M.P.H.
Co-Director, Vanderbilt Evidence-based Practice Center
Vanderbilt University Medical Center
Nashville, TN

Denise O'Connor, Ph.D.
Editor, Cochrane Effective Practice and Organization of Care Group
Australasian Cochrane Centre
Monash University
Victoria, Australia

Parminder Raina, Ph.D.
Director, McMaster University Evidence-Based Practice Center
McMaster University
Hamilton, ON, Canada

Thomas Ratko, Ph.D.
Associate Director, Blue Cross Blue Shield Evidence-Based Practice Center
Technology Evaluation Center
Washington D.C.

Gillian Sanders-Schmidler, Ph.D.
Director, Duke University Evidence-Based Practice Center
Duke University
Durham, NC

Jodi Segal, M.D., M.P.H.
Associate Director, Johns Hopkins Evidence-Based Practice Center
Johns Hopkins University School of Medicine
Baltimore, MD

Paul Shekelle, M.D., Ph.D.
Director, Southern California Evidence-Based Practice Center
RAND Corporation
Santa Monica, CA

Jonathan R. Treadwell, Ph.D.
Associate Director, ECRI Institute Evidence-Based Practice Center
ECRI Institute
Plymouth Meeting, PA

C. Michael White, Pharm.D., FCP, FCCP
Director, University of Connecticut Evidence-Based Practice Center
University of Connecticut
Hartford, CT

The Refinement of Topics for Systematic Reviews: Lessons and Recommendations From the Effective Health Care Program

Structured Abstract

Objective. The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program conducts systematic reviews on a range of health care topics. Topics are nominated by a variety of stakeholders. Nominated topics undergo a refinement process to ensure that the Key Questions are relevant, of appropriate scope, and will ultimately yield a useful systematic review. Topic refinement investigators gather input from Key Informants, topical experts, and a literature scan to inform changes in the PICOTS (population, intervention, comparator, outcomes, timing, and setting), analytic framework and Key Questions. Evidence-based Practice Centers (EPCs) have approached the topic refinement process in similar and different ways. AHRQ convened a work group to assess current approaches and to develop recommendations for best practices; we report our findings here.

Design and setting. We formed a workgroup of four investigators from four different EPCs in the United States and Canada and one AHRQ Project Officer. All participants held experience in topic refinement. We generated a prioritized list of methodological questions and possible guiding principles considered in the topic refinement process. We discussed each issue until we reached agreement.

Results. A refined topic should address an important health care question or dilemma; consider the priorities and values of relevant stakeholders; reflect the state of the science; and be consistent with systematic review research methods. The guiding principles of topic refinement are: fidelity to the original nomination, public health and/or clinical relevance, research feasibility, responsiveness to stakeholder input, reducing investigator bias, transparency, and suitable scope. We describe the mechanics of the topic refinement process, and discuss approaches and variability in methods used by EPCs to engage Key Informants, integrate and synthesize input, and report findings. Practical suggestions and challenges in preparing and recruiting Key Informants, facilitating engagement, synthesis, and reporting are described and discussed. Decisions about integrating input from various sources require investigator judgment in the application and balance of the guiding principles. The relative importance and application of these principles will vary by topic and purpose of the systematic review. Variability in topics precludes a prescriptive approach to application of the guiding principles. Transparency and consistent documentation of decisions are important for public accountability and integrity of the topic refinement process.

Conclusion. Systematic reviews that are accurate, methodologically rigorous, and as relevant and useful as possible for stakeholders require that topics be well refined. This report details guiding principles and methodological recommendations that may help investigators to better refine topics for systematic reviews, both within and outside of the EHC Program.

Introduction

"A prudent question is one-half of wisdom."
—Francis Bacon

Systematic reviews aim to improve health outcomes by developing evidence-based information about which interventions are most effective for which patients under specific circumstances, and to disseminate that information to patients, clinicians, and decisionmakers.[1] Systematic reviews are used by a variety of organizations to inform clinical guidelines,[2] health care policies,[3] and insurance coverage decisions.[4] The Evidence-based Practice Center (EPC) Program, part of the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program, conducts systematic reviews on topics related to a range of health care issues nominated by a variety of stakeholders. Stakeholders may represent patients, consumers, advocacy organizations, clinicians, researchers, agencies that issue guidelines, policymakers, industry, or health care organizations. Involving stakeholders in the nomination process provides an opportunity for end users of research to participate in asking and answering questions about health care.

To provide useful answers, systematic reviews must ask the right questions. Challenges arise when stakeholder-nominated topics are not ideally formulated for the broadest public health and/or clinical relevance, or not formulated to be researched feasibly using accepted systematic review methods. Additionally, nominations might not ideally reflect the state of the science or technical aspects of the topic. Conducting systematic reviews may be difficult or impossible for topics that are inadequately precise or overly inclusive in their description of the populations, interventions, comparators, and/or outcomes of interest. Alternatively, topics that are overly narrow might be feasibly expanded to have broader relevance than that intended in the original nomination. To ensure that systematic reviews provide the most useful answers, topics nominated by stakeholders generally need to be refined so that the Key Questions are relevant and feasibly researchable.

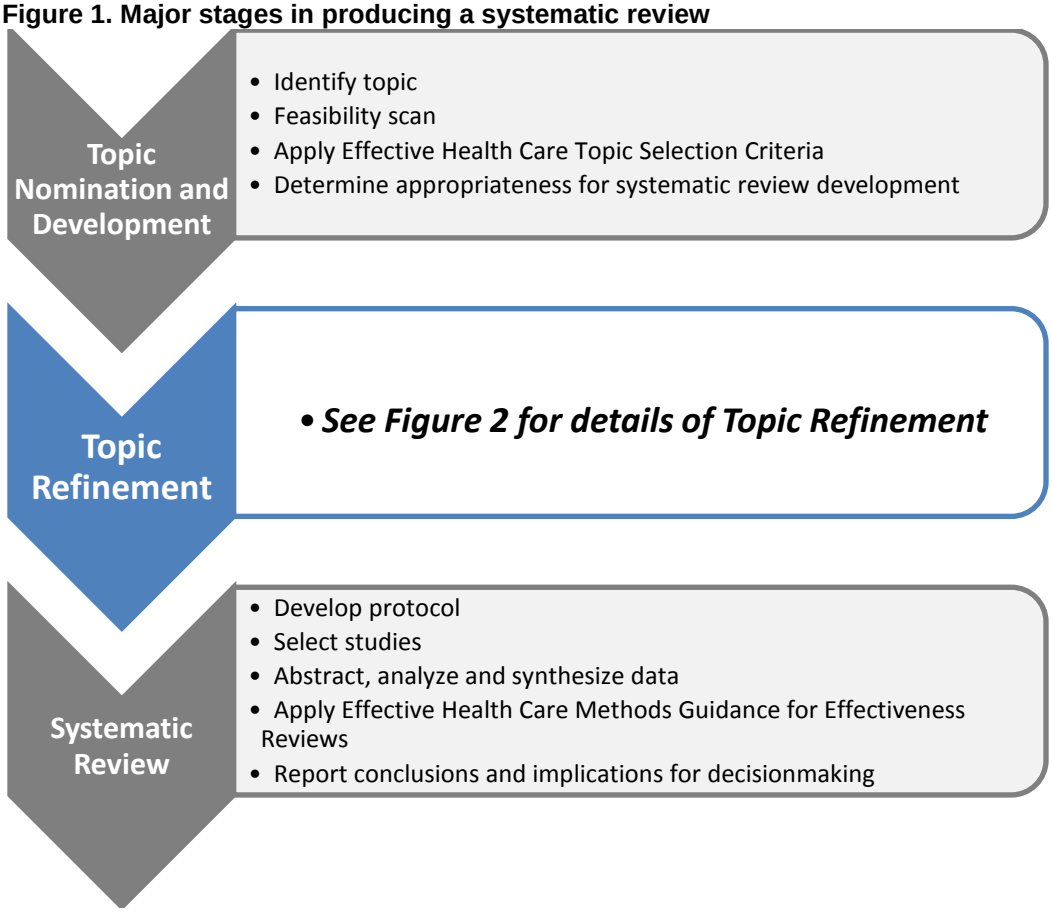
In 2007, investigators with the EPC Program began developing methods for topic refinement that were iteratively modified and eventually formalized into a Topic Refinement Document (Appendix A). Since 2009, the program has used this document as a guide for systematically conducting topic refinements and as a template for drafting summary reports for individual topic refinements. To date, this document has provided the most complete methodological guidance for topic refinement. Although the Topic Refinement Document stipulates the required phases and common elements of topic refinement, different EPCs have approached specific aspects of topic refinement in both similar and different ways. This variation among EPCs provided an excellent opportunity to learn and consider the advantages and disadvantages of different approaches to topic refinement. Therefore, AHRQ convened a work group to synthesize and assess current approaches to topic refinement and to develop methods recommendations for best practices. This report details the work group's findings, including guiding principles and methodological recommendations that may help investigators to effectively refine topics for systematic reviews, both within and outside of the EPC Program.

Background

Topic refinement is one of several major stages in the process of producing a systematic review through the EPC Program; it bridges the initial stage of topic nomination and

development and the latter stage of conducting the systematic review (see Figure 1). During topic nomination and development, a team of investigators reviews stakeholder-nominated topics and determines which nominations meet program inclusion criteria and should be recommended for topic refinement and systematic review. These recommendations are based on EPC Program principles, priority conditions, and specific selection criteria.[5] Selected topics then undergo the topic refinement process addressed in this report.

Figure 1. Major stages in producing a systematic review



The primary goal of topic refinement is to formulate research questions that can be addressed by a systematic review; the goal is not to answer the questions. A refined topic includes three principal elements: (1) clearly articulated population(s), intervention(s), comparator(s), outcome(s), timing, and setting(s) of interest—collectively referred to as the PICOTS;[5,6] (2) well-written Key Questions that are precise, detailed, and clearly focused; and (3) an analytic framework that represents the relationships between the elements of the PICOTS and the Key Questions.[7-10] The topic refinement process includes a number of steps that begin with preliminary materials from the initial topic nomination and development stage and end with the refined topic and summary report being sent to the systematic review team for use in developing the systematic review protocol. These steps are outlined in Figure 2.

Figure 2. The process of topic refinement

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; EPC = Evidence-based Practice Center; PICOTS = population, intervention, comparator, outcomes, timing, and setting

The steps of topic refinement fall into two main phases—an initial phase in preparation for interviews with Key Informants, and a second phase that starts with Key Informant interviews

and includes subsequent refinement and reporting of the topic. The Topic Refinement Document (Appendix A) provides a template for preparing a Topic Refinement Summary Report in the initial refinement phase. This is used for the Key Informant interviews and contains a narrative on the background and context of the topic, provisional PICOTS, provisional Key Questions, a provisional analytic framework, and a list of issues to discuss with the Key Informants. In preparing this report, the topic refinement team will conduct a targeted literature scan and may consult with topical experts. The Key Questions reflect important decisional dilemmas faced by stakeholders and clearly define the logic and scope of the topic. The Key Questions and analytic framework are formulated around specified PICOTS of interest. Typically, topic nominations present the elements of the PICOTS in a general form. Therefore, refining and focusing the PICOTS is a critical task of topic refinement.

Through Key Informant interviews in the second phase of refinement, the team elicits input on issues that cannot be resolved with a limited literature search and/or that require the perspective, experience, or technical knowledge of experts or other stakeholders. The Key Informants' input is considered, synthesized, and, when appropriate, incorporated into modifications of the provisional Key Questions and analytic framework, all of which is then described in the topic refinement summary report. The refined PICOTS, Key Questions, and analytic framework are posted online for broader stakeholder input before finalizing refinement. This topic refinement process typically takes about 4 months.

A Note on Terminology

In this report, we use the term **"preliminary"** to refer to elements of a topic that are developed *prior to* the topic refinement process. This includes the proposed Key Questions formulated by the nominating stakeholder and/or the topic nomination and development team. We use the term **"provisional"** to refer to the elements of the initial topic refinement phase. These "provisional" elements are: (1) descriptions of the PICOTS of interest; (2) Key Questions for the systematic review; and (3) an analytic framework. These represent the first stage of refinement, based on the work of the topic refinement team, a scan of the literature, and input from topical experts. These elements are considered provisional because they still do not include the input of multiple Key Informant stakeholders, whose views, expertise and values may lead to further refinement. Finally, we use the term **"refined"** to refer to the elements of the topic in their modified form after the topic refinement team has considered and integrated input from stakeholders (Key Informants and/or public commentary).

Objectives of the Topic Refinement Work Group

AHRQ's EPCs have produced summary reports of the refinement of approximately 100 topics for systematic reviews, using the EPC Topic Refinement Document. However, while the Topic Refinement Document stipulates the required elements to be included in the Topic Refinement Summary Report, it provides only general guidance on how to actually conduct the various steps of the process. A previous methods paper presented some guidance for topic refinement in similarly general terms.[5] With this guidance, EPCs have approached the details of topic refinement in a variety ways. This variation offered an opportunity to learn from the experience of different EPCs, to synthesize that experience into a more detailed description of the topic refinement process, and to generate more detailed guidance for this important stage in the production of systematic reviews through the EPC Program. To that end, AHRQ convened a

work group to assess the topic refinement process and develop recommendations for effective approaches to topic refinement.

The objectives of the topic refinement work group were:

1. To elaborate on the minimal and general description of topic refinement provided in the Topic Refinement Document, based on an assessment of the experience of various EPCs in conducting topic refinements.
2. To articulate a set of guiding principles for the topic refinement process.
3. Based on an assessment of the experience of various EPCs, to identify best practices and incorporate those practices into the more detailed description of topic refinement.

By producing a more detailed description of topic refinement, including guiding principles and best practices, we hope to provide useful guidance that will make the topic refinement process more consistent, deliberate, and transparent. However, we expressly did *not* seek to develop *prescriptive* recommendations to be uniformly applied in all cases. Topics vary in their requirements for refinement, and different investigators may use different but equally valid rationales to make different but equally valid topic refinement decisions. Therefore, we sought to articulate viable approaches to the numerous aspects of topic refinement and to discuss the relative advantages and disadvantages of different approaches. Rather than prescribing exactly how investigators should conduct every topic refinement, we sought to offer guidance to help EPC investigators make better decisions about how to approach topic refinement.

Methods

We convened a work group consisting of four investigators from four different EPCs in the United States and Canada and one Project Officer from AHRQ. All investigators had direct experience conducting topic refinements for the EPC Program and the Project Officer had broad experience of the topic refinement process as it has been followed across numerous EPCs. In addition, a research associate with experience as a topic refinement team project manager provided input on the logistics and management aspects of the topic refinement process.

Our work group followed previously described basic principles for developing methods guidance in the EPC program.[9] In particular, we recognized that the subjectivity and variability inherent in the topic refinement process limits the use of empirical evidence in developing guidance. Therefore, our work group used a best-practice approach based upon (1) the direct topic refinement experience of the work group members, (2) our critical assessment of completed topic refinements from other EPCs, and (3) input on an initial draft of this report from EPC investigators representing all but one AHRQ EPC.

As a first step, work group members each described their own EPC's approach to topic refinement, including their routine procedures as well as perceived strengths, challenges, and problems with the approach. The AHRQ Project Officer then described successful and unsuccessful procedures used by other EPCs not directly represented by the work group members. In this way, group members gained familiarity with the procedures of other EPCs, identifying shared practices as well as unique aspects of each EPC's topic refinement process. Next, each work group member individually reviewed three topic refinement summary reports and other pertinent documents (such as call minutes, disposition tables, and protocols) previously produced by EPCs other than their own. We compared these to elucidate: (1) similarities and differences between the elements of the original PICOTS and the Key Questions that were refined, (2) rationales used in making refinements, (3) sources of input that influenced the

decisions to refine (e.g., topic refinement team judgment, Key Informant input, literature scan), and (4) how the process was reported.

Based on these careful examinations of current practice in topic refinement, we compiled a list of questions for the work group to consider in detail. These questions addressed a range of issues and concepts that were (1) challenging for many EPCs, (2) incompletely articulated in topic refinement summary reports, and/or (3) especially variable between EPCs. We generated an initial list of 33 items, which we consolidated according to common themes into a list of 17 items for the work group to discuss. In the course of our deliberations, we further consolidated these items and categorized the relevant issues into three main categories, as presented in the Results section of this report: The overall purpose of topic refinement; guiding principles; and the mechanics of conducting a topic refinement.

We discussed each of the items during eighteen 90-minute teleconference meetings over 12 months. All meetings were audio recorded, and detailed minutes of the meetings were subsequently reviewed and discussed by all group members. When possible, the work group strove to elaborate on the basic description of topic refinement contained in the Topic Refinement Document, particularly regarding various elements of the mechanics of conducting a topic refinement such as the initial topic refinement, engaging stakeholders, synthesis, and reporting. We also strove to assess critically each item on the list and to synthesize a set of recommendations to guide the topic refinement process. We worked to achieve consensus in our recommendations regarding general guiding principles. Recognizing the legitimate variability in the requirements of different topics and in approaches to the mechanics of topic refinement, we sought to describe different viable approaches and discuss their relative merits. EPC investigators representing all but one EPC provided input on the draft report. Additional experts in systematic review were invited to provide external peer review of this draft report; AHRQ and an associated editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments and revised the final report as appropriate.

Results

The results are organized in three sections: What is Topic Refinement, Guiding Principles, and The Mechanics of Conducting a Topic Refinement. This third section combines a description of an aspect of the topic refinement process (e.g., initial topic refinement phase) with a discussion of various best practices and issues for investigators.

What is Refinement?

Refinement implies making changes to attain a better fit with a certain standard. In this sense, the goal of topic refinement is to improve a nominated topic so that it is a good and accurate fit with a number of criteria (see Box 1). A well-refined topic accurately and precisely reflects the health care question or dilemma the systematic review is intended to address. It aligns with the priorities and values of a broad range of relevant stakeholders and users of the systematic review. It should accurately reflect the state of the science and technical aspects of the topic. It should be compatible with systematic review research methods.

Box 1. Criteria that a refined topic should fit

- The **health care question or dilemma** the systematic review aims to address
- The **priorities and values of relevant stakeholders** and users of the systematic review
- The **state of the science** and technical aspects of the topic
- **Systematic review research methods**

Nominated topics may be inadequately precise, overly inclusive, or overly narrow in their descriptions of the populations, interventions, comparators, and/or outcomes of interest. Hence, refinement of a topic for public health and/or clinical relevance and for research feasibility may involve narrowing the focus of some elements of the PICOTS, expanding some elements, or both. This process more closely resembles sculpting in clay than sculpting in marble.

Topic refinement investigators strive to optimize the fit of the topic with all of the categories in Box 1. To do so may require a balanced compromise that considers the relative importance and/or practicality of the criteria. For example, certain stakeholders might nominate a topic highly relevant for their own constituency but also very narrowly focused. A topic refinement investigator might recognize the potential for viably expanding the focus of such a topic to be more broadly relevant to other stakeholder groups, with little or no reduction in relevance to the nominating group. At the same time, the results of a literature scan might suggest that certain aspects of the question have already been adequately answered and therefore should not be included in a new review. Decisions that produce relevant and researchable (and therefore useful) Key Questions lie at the heart of the topic refinement process.

Guiding Principles

In refining a topic, investigators make numerous decisions to include, exclude, or otherwise modify aspects of the populations, interventions, comparators, outcomes, and settings of interest. They also decide how these elements of the PICOTS should relate to one another as formulated in the Key Questions and analytic framework. Our reviews and discussion of previous topic refinements suggested that investigators variably consider and apply principles when making decisions and refinements; however, the basis upon which these decisions are made has not been previously formalized.

We identified seven guiding principles to be routinely and systematically considered in the course of refining a nominated topic for a systematic review (see Box 2). These are: (1) fidelity to the original nomination; (2) relevance; (3) research feasibility; (4) responsiveness to stakeholder input; (5) reducing investigator bias; (6) transparency, and (7) suitable scope. Four principles (fidelity, responsiveness, minimizing investigator bias, and transparency) relate primarily to the conduct of the topic refinement process, and three relate more to the topics themselves (relevance, research feasibility, and suitable scope). These inter-related principles for topic refinement are consistent with those previously described in the EPC guidance for conducting systematic reviews, including relevance, timeliness, objectivity, scientific rigor, public participation, transparency, and emphasis of a patient-centered perspective.[11]

Box 2. Guiding principles for topic refinement

- **Fidelity to the original nomination** retains the essential intent of the nominator and does not necessarily strive to satisfy the specific purpose of a given nominator. This assures that topics and systematic reviews are based on real-world issues that are important to stakeholders and that the systematic review will have relevance to a ready audience.
- Topics have **relevance** to those who would make decisions with the findings of the systematic review, as well as those who would be affected by those decisions.
- **Research feasibility** pertains to the practicality of conducting a review using systematic review methods within available resources.
- **Responsiveness to stakeholder input** assures that topics are tied to real-world concerns and decisional dilemmas, but does not require integration of all input.
- Each investigator brings their experience, expertise, perspective and values, which could introduce bias. Aspects of the topic refinement process can **reduce possible investigator bias**.
- **Transparency** in reporting includes a clear description of topic refinement decisions and the underlying rationale. This is important for public accountability and the integrity of the topic refinement process.
- A topic scope is the degree of inclusiveness reflected in the PICOTS, Key Questions and analytic framework. Defining a **suitable scope** for a topic requires the investigator to consider numerous factors that affect the complexity and level of detail of the Key Questions.

To satisfy a certain principle an investigator may have to compromise on satisfying another principle. For example, to increase the relevance of a nominated topic that specified a very limited population or setting an investigator might substantially broaden the scope of the PICOTS. In turn, this broader scope might reduce the feasibility of researching the topic. Given that topics vary widely, the relative importance of each principle may also vary according to the topic being refined. Hence, these recommendations are not meant to prescribe *how* these principles should be applied or balanced for individual topics, only that they *be* considered. Inevitably, skilled investigators will use their judgment and discretion in refining topics, often making trade-offs between various objectives. We envision investigators using the following seven guiding principles for more systematic and explicit decisionmaking.

Fidelity to the Original Nomination

The EHC Program is committed to addressing patient-centered health care questions that are tied to the concerns and decisional dilemmas of a broad range of stakeholders—from patients to advocacy groups to professional societies. And while the program does not necessarily strive to satisfy the specific purposes of given nominators, maintaining fidelity to the original nomination assures that topics and systematic reviews are based on real-world issues that are important to stakeholders. Fidelity to the nomination also assures that the systematic review will have relevance to a ready audience. Topic refinement might change the PICOTS and with them the aims of the review. Investigators should be mindful of the initial intent of the nominator as they narrow or broaden a topic so that the resulting review can be useful to a broad range of stakeholders.

Relevance

Topics should be relevant to decisional issues that matter to the users of the systematic review, and should include outcomes that matter to patients even when the evidence may be scarce.[12] Some nominated topics of high relevance to the nominator may be too narrowly framed to be of great use to a broader audience. Thus, topic refinement investigators may broaden or change the scope of the topic to increase its relevance. For example, in the original nomination of a topic on the effectiveness of case management[13] the nominator specified case management

performed by certified nurse case managers. The literature scan and input from Key Informants suggested that case management is frequently conducted by nurses without special certification and by professionals other than nurses. Therefore, the topic was expanded to be more broadly inclusive and relevant to a wider variety of case managers (while maintaining fidelity to the original nomination).

The investigator refines the topic to reflect the underlying clinical logic, which includes the relevant clinical concepts and beliefs about the mechanism by which interventions may improve health outcomes[9]. This requires an understanding of the relative strengths and weaknesses of the arguments for (1) including particular populations, interventions, comparators, outcomes and settings, and (2) the proposed relationships between these elements. This understanding should be reflected in the analytic framework and Key Questions. A topic might be *generally* relevant for a particular issue or audience, but its relevance is limited if the details of the formulated analytic framework and Key Questions do not reflect the intrinsic clinical logic of the topic. For example, the original nomination for a topic on the treatment of pressure ulcers[14] included as an outcome the progression of an ulcer to a more advanced stage. Key Informants emphasized that traditional staging systems imply a natural progression in wound severity that ignores variability in etiology. They also emphasized that progression of stage may not always be a relevant outcome. Therefore, the refined topic did not include progression of stage as an explicit outcome of interest.

Research Feasibility

Research feasibility pertains to the practicality of conducting a review using systematic review methods within a specified timeframe and budget. Factors that affect research feasibility are the complexity of the health care issue of interest; the clarity and precision of the Key Questions; the relative heterogeneity of the PICOTS elements; the scope of the topic; and the size and nature of the evidence base.

Key questions that explicitly address the clinical logic and complex aspects of a topic enhance the feasibility and improve the usefulness of the systematic review. For example, a topic was originally nominated in very general terms as "Can screening and surveillance for colorectal cancer using fecal DNA analysis improve health outcomes?"[15] As nominated, this topic did not reflect the underlying complexity of the issue. To make the clinical logic of the topic explicit, the team included Key Questions and an analytic framework that addressed test characteristics, test performance compared with established screening methods, acceptability and adherence to testing, optimal screening intervals, impact on patient-centered outcomes, and harms. Making these important aspects of the topic explicit enhanced its research feasibility.

The clarity and precision of the Key Questions and PICOTS directly influence systematic review inclusion and exclusion criteria. Questions that are unclear or vague may be cumbersome or too complex to answer. Precise Key Questions allow for clearer decisions about the evidence and its synthesis, producing more accurate and efficient reviews. Similarly, the heterogeneity of the PICOTS may also affect research feasibility. A topic that includes diverse populations, interventions, outcomes and/or settings may be more cumbersome to research. A heterogeneous mix of PICOTS and Key Questions may make evidence synthesis more complicated and presentation of the findings less clear.

The scope of a topic may also affect research feasibility. If a topic addresses numerous health care issues, or aspects of an issue, the synthesis of the evidence and communication of findings may be challenging. The topic refinement team may have to decide whether to conduct one

systematic review should include them all or multiple more narrowly focused reviews. Such decisions should consider whether a high degree of inclusiveness would allow for clear and precise Key Questions, and whether a lower degree of inclusiveness would reduce relevance for decisionmaking.

Closely related is the influence of the evidence base. If the evidence base is large, it may be unwieldy and impractical to extract and synthesize the relevant literature within available resources. This might suggest the need to split the topic into multiple reviews, or to further focus and narrow the Key Questions. Investigators should consider whether such refinements would reduce the relevance of the review. Conversely, a small evidence base does not necessarily imply that the topic is not feasibly researchable. If certain questions are deemed highly relevant for important decisional dilemmas, then characterizing the evidence base—even if it is lacking—may be useful. Other aspects of the evidence base may also affect research feasibility, such as the design and quality of included studies.

As an example, an original nomination that included both screening for hepatitis C virus (a population health question) and treatment of hepatitis C virus (an individual health question) was refined and divided into two separate systematic reviews due to complexity of the Key Questions, volume of literature, and timeliness of review.[16,17] Key Informants emphasized the importance of understanding treatment effects, and inclusion of new treatment regimens and testing options. The Key Questions were revised to capture the complexities raised by Key Informants, and significantly expanded the scope of the review. To feasibly and adequately review the literature in a timely fashion at the level of detail emphasized by stakeholders, two separate reviews were developed in tandem.

Responsiveness to Stakeholder Input

To assure that topics are tied to real-world concerns and decisional dilemmas, the topic refinement team is responsive to the input of stakeholders, including those making public comments. Key Informants may differ in their perspectives, understanding, values, and priorities about the health care issues. It is not a goal of topic refinement to reach consensus among stakeholders. Consensus may arise spontaneously, suggesting that the PICOTS and Key Questions are on target. However, a lack of consensus may be equally useful in highlighting an area of disagreement that the team may further explore before making a refinement decision.

By considering the viewpoints and priorities of a broad range of stakeholders, the team may reduce the potential bias of singular views and avoid investigator tunnel vision. This does not imply, however, that the topic refinement team must comply with or incorporate all stakeholder input. Stakeholders can provide the investigators with a diversity of perspectives to consider, but the ultimate topic refinement decisions belong to the topic refinement team.

Reducing Investigator Bias

A topic refinement investigator serves as an arbiter who weighs and integrates information and viewpoints from various sources (literature, topical experts, and Key Informants). Each investigator also brings their experience, expertise, perspective, and values, which could bias the process. Numerous aspects of the topic refinement process can reduce the possible effect of investigator bias. First, as a deliberative process among members of a team, the assumptions and viewpoints of investigators can be made explicit and discussed. In this way, the team can become aware of their possible biases. This awareness allows them to more easily consider their views in relation to other input garnered during topic refinement. The deliberative nature of the process

also facilitates the explicit consideration of possibly conflicting views of experts and/or stakeholders. Second, the EHC Program enforces a conflict of interest policy for investigators.[18] Third, a topic refinement team considers input from diverse stakeholders whose viewpoints and priorities may challenge the assumptions of investigators, identify gaps or inconsistencies in thinking, and provide insight into different values related to the questions of interest. Finally, topic refinement is a structured process that formalizes the steps of gathering and processing information, making refinement decisions, and transparently reporting those decisions. The consistency and structure of the process can help to assure that topic refinement investigators openly and judiciously consider various relevant viewpoints, including those that are new or different than their own.

Transparency

The evidence that influenced crucial topic refinement decisions and the rationale underlying critical refinements should be clearly and explicitly described and documented. This principle is important for public accountability, scientific rigor, and efficiency in the subsequent steps of conducting the systematic review.

Whitlock et al.[5] described public accountability as an ethical requirement for topic identification and selection in the EHC Program, because EHC decisions affect the allocation of limited public resources for comparative effectiveness research. The same principle and rationale apply to the topic refinement process. Stakeholders will have different perspectives and priorities regarding a given topic. Interested parties should be able to determine if and how their priorities were considered in the topic refinement process. Not all stakeholder input will necessarily have been included in the topic refinement process, but transparency allows for public accountability.

Transparency in reporting can also provide important insight into how the research process affected the outcome. The unavoidable subjectivity in the topic refinement process precludes its replication as in a controlled experiment. Yet, this same element of subjectivity makes transparent reporting all the more desirable for a rigorous process. The judgment and discretion of individual investigators will always come into play. This implies that two investigators or topic refinement teams presented with the same original topic nomination could make different decisions and refinements and thereby produce two topics with different PICOTS and Key Questions from a single original topic. Documenting the influence of specific assumptions, evidence, stakeholder input, and rationales allows a critical reviewer or a stakeholder to understand the basis upon which particular refinements to the topic were made.

Transparent documentation of the topic refinement process can also be of value in the subsequent stages of the systematic review. A clear record of the topic's evolution that describes the factors and thinking behind refinements can improve the efficiency and coherence of the systematic review process. This helps to prevent unnecessary duplication of effort on previously addressed questions while providing background context in light of which new questions can be considered.

Summary reports from different EPCs have displayed considerable variability in the detail and transparency of documentation. To make these reports more reliably transparent, we recommended changes to the Topic Refinement Document, including more explicit instructions and a structured guide for more complete reporting of the evolution of the topic. These changes have been incorporated into an updated document (Appendix A) and are described in the section on "Reporting," below.

Suitable Scope

The scope of a topic refers to its relative degree of inclusiveness as reflected in the PICOTS, Key Questions, and analytic framework. The designated scope of a topic is related to a variety of factors, including the topic's intended relevance and research feasibility. A topic of narrow scope might be restricted to a single form of an intervention in a particular subpopulation with one outcome of interest and a single setting; it may lack the most relevance. In contrast, a topic of broad scope might include various forms of the intervention in the general population and include multiple outcomes and settings; it may present challenges for research feasibility. A suitable scope is sufficiently inclusive to have high relevance and usefulness for decisionmakers, and yet is not so broad as to reduce the coherence of the review and the precision of its findings.

The scope may also vary according to the complexity of the PICOTS elements and their interrelationships as expressed in the Key Questions. For example, a topic on the use of disease-modifying antirheumatic drugs (DMARDs) for treatment of juvenile idiopathic arthritis (JIA)[19] included multiple types of DMARD and multiple subtypes of JIA. In addition to the breadth of scope directly related to including numerous interventions (DMARDs) and numerous subpopulations (JIA subtypes), the scope of the topic was further broadened to include the question of variable effectiveness of different DMARDs with different JIA subtypes.

The scope of a topic may also be a function of the level of detail in the Key Questions. In general, higher specificity and detail in the PICOTS and Key Questions will constrain the focus of the topic and limit its scope. That is not to say that a topic with highly detailed Key Questions is always of narrow scope, as a topic of broad scope by virtue of addressing numerous issues with many Key Questions might have a high level of detail in those questions. Scope is distinct from the other principles, in that a description of the suitable scope is a *goal* of topic refinement and not a principle, per se. However, refinement decisions must usually consider scope in much the same way as the other principles.

Other Programmatic Considerations

The three major stages of a topic in the EPC program (topic nomination and development, topic refinement, and systematic review) are guided by separate but complementary criteria and principles. Infrequently, the topic refinement team may discover (perhaps through input from Key Informants or a more detailed literature scan) that that the topic as proposed no longer fulfills the program's selection criteria. Even though the considerations and purposes of topic development and topic refinement are separate and distinct, a topic in the refinement period must still fulfill the original selection criteria. If the topic cannot be reframed to fulfill the selection criteria it may not proceed to a systematic review.

Similarly the topic refinement team is mindful of the principles for the conduct of the systematic review. The application of topic refinement guiding principles can facilitate the principles for the conduct of the systematic review. Exercising the principles of responsiveness and relevance can promote a patient-centered approach to the evidence. The engagement of relevant stakeholders can elucidate the clinical logic. For example, during the topic refinement process for point-of-care testing for hemoglobin A1c (HbA1c), the topic refinement team learned that another systematic review on the same topic was underway.[20] The Key Informants felt that it answered their questions; it was the decision by the team and AHRQ that a new systematic review on this topic would be duplicative and would not add to the current body of knowledge.

In another example, the topic refinement team for enzyme replacement therapy for lysosomal storage disease[21] discovered that evidence was limited for the relevant outcomes for this rare

condition. The team weighed several factors in addition to the small body of evidence on long-term effectiveness and harms, such as the inclusion of many study types (small trials, case series, and case reports) and the high potential for impact (affirmed by the absence of systematic reviews and by the Key Informants). Considering these factors, the team proceeded with a different type of EPC report, a technology brief, rather than a systematic review. The alternative report was more appropriate for the volume of the literature and the state of the science, while still providing information that would be relevant, timely, and useful for decisionmakers.

The Mechanics of Conducting a Topic Refinement

During topic refinement in the EHC Program, nominated topics are ushered through several phases (Figure 2). Although the essential phases of the process follow a logical temporal sequence, the resulting changes in the topic may not always flow in a linear and predictable way. The outcome of one phase (e.g., Key Informant interviews) may lead to a revision in the outcome of a previous phase (e.g., Key Questions developed in the initial topic refinement). Certain aspects of the topic will fall into place before others, in no set order. Furthermore, the details of how a given phase of the process is conducted will differ depending on the nature and requirements of the particular topic; the skills, expertise, and experience of the topic refinement team; the particular Key Informants; and the resources of the individual EPC. Investigators must apply judgment and discretion when planning and conducting the various phases of the process.

The degree of refinement required will vary across topics. Some topics begin with clear and relevant Key Questions and well-defined PICOTS that accurately reflect the clinical logic; in these cases little may change during the topic refinement stage. Other topics may be less clear or complete and require more substantial refinement. In either case, all topics undergo the entire topic refinement process.

The Topic Refinement Team

Topic refinement requires a variety of skills. Members of the team should have (1) expertise in the methods of systematic review research, (2) knowledge of health care and/or health services, (3) the ability to search and understand health care research literature, (4) the ability to converse fluently with topical experts, (5) the ability to effectively engage stakeholders, (6) skill in the methods described in this report, and (7) project management skills. In addition, a topic refinement team needs to have knowledge of the particular health care topic of interest. It is not expected that each or any member of the team will have all of these skills, just that they have the skills collectively as a team.

EPCs have configured their topic refinement teams in different ways. Teams may include one or more investigators (M.D. or Ph.D.), one or more research associates/assistants, and a research librarian. Depending on the topic, this core team might be supplemented with a topical expert and/or a statistician. Some EPCs use a dedicated core team that leads all of the EPC's topic refinements. Other EPCs employ a single team to lead both topic refinement and the systematic review. Each approach has its own advantages and disadvantages, and EPCs should consider which approach best suits their organization and resources.

The use of a dedicated topic refinement team has the advantages of consistency, efficiency, and iteratively improved expertise. An experienced team that has conducted multiple topic refinements may acquire finer skills in the topic refinement process. In addition, having a dedicated topic refinement team may help to clearly distinguish the different objectives of the refinement stage and the systematic review stage. The goal of topic refinement is to formulate

the questions, and the goal of the systematic review is to answer those questions. When formulating the questions it is important not to let considerations of the possible answers overly influence the formulation of the questions. This may be more difficult to achieve if the refinement and systematic review teams are the same.

An advantage to using a single team is improved continuity and efficiency throughout the topic refinement and systematic review process. When the systematic review commences, the team will already be familiar with the topic, facilitating the transition from the topic refinement phase to the systematic review phase. In addition, if further evolution of the Key Questions, analytic framework, and PICOTS is needed the team will be familiar with the issues considered during refinement, which may facilitate decisions about any additional changes to the topic. EPCs using a dedicated topic refinement team approach have addressed this need for continuity between the stages by including at least one of the topic's systematic review investigators as a member of the refinement team.

Initial Topic Refinement Phase

During the initial topic refinement phase, the topic refinement team will conduct an additional literature scan to supplement the guidance compiled during topic nomination and development. The purpose of this literature scan is two-fold: (1) to help the investigators better understand the topic, its clinical logic, and the decisional dilemmas; and (2) to familiarize the team with the extent of the relevant literature. The literature scan is a targeted search and review of the evidence, which is not fully synthesized. The intent of the literature scan is to provide insight about the research feasibility, relevance, and scope of the subsequent systematic review.

The members of the topic refinement team will not necessarily be experts in the topic, in which case they may conduct informational interviews with topical experts. These interviews provide insight into technical issues, controversies, and the current state of knowledge about the topic. Specific interview questions should be crafted to help clarify basic issues of the topic or uncertainties that arise in the course of reviewing the topic nomination materials and the literature scan.

Guided by a literature scan, input from topical experts, and discussions among themselves, the team develops the provisional PICOTS, analytic framework, and Key Questions. These provisional forms of the essential topic elements will then be used as the basis for interviews with the Key Informant panel (described below). The PICOTS, analytic framework, and Key Questions are interdependent and complementary, and usually evolve together—with changes in one usually carrying through to the others.

Appendix B provides an example from an actual review to illustrate the refinement of a few aspects of a topic. Figure B1 shows the changes to the preliminary nominated PICO (without Timing or Setting) and the nominated question of interest as they were refined into their provisional form. Table B1 charts the identified need for changes to particular elements of the nominated topic, the changes that were made, and the rationale for the refinements. This appendix does not provide a comprehensive description of the entire refinement of the topic. Rather, it illustrates a systematic approach to refining a select few aspects of a single topic. Such an approach can be comprehensively applied to the initial refinement of all aspects of a given topic.

PICOTS

The provisional PICOTS should be patient-centered and relevant for decisionmaking, regardless of what the topic refinement team anticipates will be found in the current literature.[5] For example, outcomes that matter most to patients, such as quality of life or morbidity, are generally more important than intermediate outcomes such as biomarker values. And, comparators that reflect real-world clinical practice or standard of care (and hence are relevant to decisionmaking) are generally preferable to placebo or no treatment.

Refining the PICOTS often involves a balance and tradeoffs between the different PICOTS elements; i.e., inclusion of one element might have restrictive implications for other elements. For example, an outcome of particular interest may not be applicable to certain subpopulations; or constraining the population of interest may limit the relevance to certain interventions. When making refinement decisions about the PICOTS, the topic refinement team considers the principles discussed above, including fidelity to the nomination, scope, relevance, and research feasibility.

The Analytic Framework

The analytic framework illustrates the relationships between the PICOTS and the Key Questions; these inform the systematic review scope and inclusion criteria. This can be useful for both the investigators and the end users of the systematic review—especially when the questions represent a complex logic chain—because the framework highlights the decisional context of Key Questions. The analytic framework depicts our understanding and assumptions of the clinical, biological, or health services underpinnings of the mechanisms through which an intervention is presumed to affect outcomes. Patient-centered outcomes occupy the final causal position in the framework. Causal intermediates or surrogates of the primary outcomes are shown more proximally in the framework. These "intermediate outcomes" are important if associated with patient-centered health outcomes or important for decisionmaking.

The choice of patient-centered and intermediate outcomes reflects the priorities and values of stakeholders and the clinical logic of the topic. An understanding of the clinical logic may come from the literature scan, input by topical experts, and/or the topic refinement investigator's expertise. This may be affirmed or revised later by input from Key Informants or public commentary. The analytic framework has been described in more detail previously.[7-10] An example of an analytic framework is in Appendix B.

Key Questions

The Key Questions guide the systematic review. As with the analytic framework, the Key Questions reflect the clinical logic and the important decisional dilemmas of the topic. A fundamental goal of topic refinement is to formulate precise, detailed, and clearly focused Key Questions that elucidate the health care issue of interest. At a minimum, the questions explicitly include the basic elements of population(s), intervention(s), comparator(s), and outcome(s) (PICO). They may also include timing and setting (TS). Each element of the PICOTS and their respective relationships should be specifically and unambiguously described.

Good Key Questions are formulated without judgments about the likelihood of the extant literature to answer them. The Key Questions address patient-centered health outcomes (e.g., quality of life, mortality, hospitalization rates), intermediate outcomes (e.g., diagnostic test characteristics, biomarker values), harms, and factors that may influence effect estimates and introduce heterogeneity in results. To investigate these factors, investigators may include

additional Key Questions about subpopulations, different forms of the intervention, or specific settings. See Appendix B for an example of provisional Key Questions.

Engaging Stakeholders as Key Informants

The topic refinement team obtains input from stakeholder groups through the engagement of Key Informants. The Key Informant panel is a small number of individuals, who reflect the perspectives of those who would make decisions with the findings of the report, as well as those who would be affected by those decisions. Key Informant input can improve the systematic review, help ensure that the research reflects the needs of diverse groups, and facilitate the diffusion and implementation of findings.

Key Informants provide:

- Opinions about the preliminary Key Questions, PICOTS and analytic framework.
- Input about issues not adequately addressed in the initial topic refinement phase.
- A spectrum of relevant views about technical aspects of the topic, stakeholder priorities, standards of care and potential dilemmas or controversial decision points.
- Input about the most important outcomes for decisionmaking.

Key Informants also provide input from diverse viewpoints. For example these individuals may: describe their experiences with a particular technology; share their opinions about the advantages or disadvantages about specific treatments; describe usual care from the perspective of their organization or specialty; share their opinions about the contribution of the proposed systematic review in improving health care; and/or elucidate important factors and values that affect their decisionmaking (see Appendix A for additional detail). With this input the topic refinement team can better understand real-world context; decisional dilemmas from a variety of perspectives; and controversies and reasons for divergent views. This in turn helps to inform the scope of the review, and improves the relevance and applicability of the results of the evidence review for decisionmakers.

Identifying and Recruiting Key Informants

The topic refinement team first identifies relevant stakeholder categories for the Key Informant panel. The team should ensure that the Key Informants represent the diversity of viewpoints on the topic. Unless clearly not relevant for a particular topic, patients or their representatives should always be included. The importance of other stakeholder groups will vary according to the topic and the particular issues or dilemmas to be considered. For topics known to be controversial or associated with particularly challenging dilemmas, Key Informants representing the important opposing viewpoints should be enlisted. Although the number of Key Informants varies by topic and the nature of the questions of interest, the typical range has been 6 to 12 individuals.

The topic refinement team may have a preliminary list of stakeholders from the topic nomination development phase. Key Informants might be identified by contacting professional, industry, or advocacy organizations; by contacting experts whose publications are identified in the literature scan; by referral of the AHRQ Project Officer, who may know of relevant stakeholders who have participated in the EHC Program; by referral of topical experts; or by referral of potential Key Informants (both those who elect to participate and those who do not).

Recruitment and scheduling of Key Informant interviews can be time consuming. Generally it requires multiple communications and coordination of schedules. Some potential Key

Informants will decline to participate or will be unavailable during the designated timeframe. Therefore, making a prioritized list of more than one potential candidate for each stakeholder category is helpful. The initial invitation to participate should include a brief introduction to the EHC Program and their role in the topic refinement process; a description of the topic and the interview process; and information about the time and preparation required to participate.

Composition of Key Informant Interview Groups

The topic refinement team considers various factors when grouping Key Informants for interviews. These factors include the number of individuals, the types and variety of stakeholder groups, and the specific issues to be addressed. Determining the desired composition of the groups for individual interviews requires the judgment of the topic refinement investigators. For example, if the interview were to focus primarily on an issue requiring particular expertise, the size and heterogeneity of the group could be limited. Similarly, if the topic refinement investigators sought to explore the tension between differing views of an issue, a larger and more heterogeneous group might be desirable (e.g., a patient advocate, a clinician, and an industry representative). Patients or consumers may be more comfortable expressing their views when in a single stakeholder group. The team should carefully consider the type of information needed to further refine the topic and then compose the individual Key Informant interview groups accordingly.

The size of the group in a single interview may affect the quality of engagement, the detail and depth of the discussion, and the ease of facilitating the interview. An overly large group may not allow for all Key Informants to fully express their views within the allotted time. Similarly, trying to hear from too many participants and to address all questions on the interview agenda may preclude exploration of a particular question to the desired level of detail. Compared with smaller groups, a large group is more likely to include participants with a wider diversity of opinions, personalities, and communication styles, all of which may challenge the interviewer's ability to guide and focus the discussion. Larger groups might be viable if the issues for discussion are limited and the Key Informant group is sufficiently homogeneous. Larger groups do offer the potential advantage of reducing the time demand on the topic refinement team; but this advantage may not outweigh the disadvantages.

Determining the best size and composition of interview groups involves balancing the factors mentioned above with practical considerations such as the interview timeframe, schedules of the Key Informants, and available time of the topic refinement team. In our experience, two to four Key Informants per interview is effective and efficient for most topics. For eliciting very specialized and/or voluminous information, one-on-one interviews with particular individuals may be beneficial.

Conducting Key Informant Interviews

Key Informant interviews provide a means for the topic refinement team to gather information and better understand stakeholder opinions, values, and priorities. Consensus among participants however is not the goal. Generally, the team conducts interviews over a period of about 3 to 4 weeks, followed by several additional weeks to synthesize and incorporate input. The interviews are not conducted with the same high level of methodological and analytical rigor that would be used in focus group research (e.g., coding of transcripts, reaching saturation). Rather, they are an efficient way of eliciting input from stakeholders in as complete and thorough a manner as possible within the practical timeframe of the overall systematic review process.

The interviews are usually conducted via teleconferencing, although face-to-face interviews are sometimes possible. The interviews are scheduled to allow adequate time (typically about 60 to 90 minutes). Oftentimes a core member of the topic refinement team facilitates the interviews. Adequate preparation is essential to successful Key Informant interviews. Key Informants are sent advance materials that review the general purpose of topic refinement and clarify their role in the process; the provisional PICOTS, Key Questions, and analytic framework; and a list of the salient issues and questions to structure and guide the discussion. The list should also include open-ended, jargon-free questions that invite input on any aspect of the topic.

In preparation, the topic refinement team generates a well-considered list of clear and specific discussion questions to guide and structure the interviews. These should be questions about which the team is uncertain and/or which require the input of particular stakeholders. These may be questions that the team has not been able to adequately address with the literature search or in discussion with topical experts, or they may be questions that require additional stakeholders' perspectives, experience, or viewpoints. Questions that explicitly invite comments on the provisional PICOTS, analytic framework and Key Questions can provide useful input that might not emerge spontaneously. In particular, a question about which outcomes are important for stakeholders in making decisions can improve the relevance of the systematic review. And, asking for general input not specific to prepared questions may elicit important unanticipated perspectives.

The facilitator may open the interview by briefly reviewing the essential information contained in the preparatory materials. Such an introductory review will help clarify the goals of the interview, the meaning of PICOTS, the analytic framework, etc. Effective facilitation is essential for effective Key Informant interviews, and the general principles of effective facilitation have been described elsewhere.[12] Critical elements of good facilitation include assuring that all participants are included and allowed to fully express their views; posing effective followup questions that clarify and/or probe the subject more deeply; synthesizing various contributions and advancing the discussion by reformulating questions or just moving to the next agenda item; and reserving one's own opinion beyond that required to elicit and explore the views of the participants. Ultimately, effective facilitation requires good familiarity with the topic and the issues faced in the initial refinement.

The facilitator's job can be more challenging if the group is heterogeneous, either by design or circumstance. Generally, for a more diverse mix of Key Informants, the facilitator should emphasize questions at the intersection of the participants' varied backgrounds. For example, in an interview that includes a patient advocate and a clinician, the facilitator should avoid medical jargon and technical issues and emphasize questions for which all group members can be expected to have an opinion on an equal basis.

A detailed record of the interviews can be useful for reliably considering all relevant input. Such a record also aids the team in producing a summary report that accurately depicts the interviews and the decisions reached by the team. Various methods are used across EPCs to document the content of Key Informant discussions. Typically minutes are taken of interviews and circulated to participants. Recording and transcribing the interviews provides an even more complete record. Team members from at least one EPC use a standard form for this purpose. The form includes sections for (1) recording participants' input related to specific PICOTS elements, (2) observations and thoughts of the team member, and (3) questions as to whether any issues raised should be incorporated into future interviews and/or warrant specific refinements to the

topic. It provides a structure for debriefing after the interview and helps ensure that important issues are not missed in the synthesis once all the interviews have been completed.

Integration and Synthesis

An essential aspect of the topic refinement process is the integration and synthesis of the information that the team gathers from various sources (literature scan, topical experts, and Key Informants). They consider whether to integrate this input, and how it will affect the analytic framework, Key Questions and PICOTS. These decisions about integration and synthesis are informed by the guiding principles. The importance of each principle may vary by topic, and the team will consider the extent to which a principle is applied, and the balance of one principle with another. Although this report describes effective practices and approaches to topic refinement, the variability between topics makes it impractical to apply the principles in a prescriptive manner. Some issues of synthesis were mentioned in the guiding principles section; this section discusses in greater detail how topic refinement investigators may balance specific principles.

Some refinement decisions are straightforward, and the team may incorporate information that addresses those issues in the course of gathering the information. For example, a nomination might not specify all subclasses of an intervention drug of interest, and the team might easily clarify with the literature scan or topical expert that an additional subclass is also clearly relevant. For other issues the team may intentionally delay a decision to gather additional input because the issue is complex, controversial, or best addressed by another source of information. For example, a Key Informant might indicate that a proposed outcome measure is not appropriate even though the literature scan showed that the measure is commonly used. In such a case, the team might wait to discuss the issue with subsequent Key Informants and/or topical experts before making a decision. Occasionally an issue previously settled is reconsidered in light of additional information or a subsequent decision about another issue.

The team may encounter various challenges in deciding how to synthesize different information, particularly when sources of input conflict. Differences may arise between the original nomination and Key Informant input. For example, the topic nominator may intend to use the systematic review as the foundation of a clinical guideline, and will specify particular interventions. Key Informants may identify additional interventions and comparators that reflect clinical practice and decisional dilemmas. The team will then balance fidelity to the original nomination with responsiveness to stakeholder input and suitable scope to ensure that the systematic review is relevant and useful to the nominator and for other stakeholders.

In other instances Key Informants may disagree on an issue. The team cannot be responsive to all input, and must judiciously decide which input to integrate. In making these decisions, the topic refinement investigator can consider the nature of the evidence, the opinions of experts, the team's own expertise with the topic and/or systematic review methods, and other EHC program principles such as patient-centeredness and public health relevance.

If a topic is limited in its scope by the needs of the nominator or input from Key Informants, the literature scan might reveal a small evidence base, in which case the team may have to balance the research feasibility of the topic with programmatic considerations about the broader relevance and usefulness of the proposed review. In other cases, the literature scan may reveal a large evidence base after further refinement of the clinical logic with Key Informant input; and the team may have to balance responsiveness to stakeholder input, research feasibility, and suitable scope to yield a useful and timely review.

Reporting

The multiple opportunities for modifying a topic underscore the importance of consistently reporting decisions and the team's rationale for those decisions. This is important for the topic refinement team, for AHRQ, and for other EPC colleagues who may undertake the topic when it proceeds to the evidence review phase.

The topic refinement summary report documents the evolution of a topic through the refinement process, and may be used as a reference throughout the lifecycle of the topic in the EHC program. The topic refinement team may use this document for internal communication about reasons for changes through the topic refinement process. For the evidence review team, the topic refinement summary report may provide an historical document to understand previous decisions, inform discussion of similar issues, accurately respond to the Technical Expert Panel or peer reviewers about decisions made during topic refinement, assist with framing controversial issues in the evidence report, and contribute to discussion of future research needs in the evidence report. The AHRQ program officer may refer to this document to respond to stakeholder queries and to ensure consistency with EHC principles and criteria.

Generally the topic refinement summary report:

- Documents the evolution of a topic and explains refinement decisions, particularly when there is a clear alternative.
- Summarizes input from topical experts, Key Informants, the literature scan, and public reporting.
- Documents responses to input
- Points to areas of conflicting input.
- Highlights areas that remain unresolved.

Historically, the topic refinement summary reports have not included formal documentation of changes made after public posting of the draft Key Questions, PICOTS and analytic framework; or details of the initial literature scan. These changes are reported in other documents generated during the topic refinement process.

The workgroup observed variability in the content and level of detail in individual summary reports in the following areas:

- Documentation of topical expert discussions.
- Key Informant input, though much greater detail was found in the Key Informant call minutes.
- Documentation of changes to Key Questions and PICOTS.
- The rationale for changes to Key Questions and PICOTS, especially those made prior to Key Informant input.
- Description of decisional issues or controversies, and how different priorities or inputs were considered by the topic refinement team.
- Documentation of considerations given to the literature search.

The workgroup noted that other documents generated in the course of topic refinement (e.g., call minutes with the Project Officer and Key Informants) sometimes provided highly detailed documentation of discussions. However, the topic refinement summary reports frequently did not capture sufficient detail about the important issues and decisions that affected the topic scope.

While transparency does not require detailed documentation of every change and step in the process, disclosure is important for establishing confidence in the refined document—the

confidence of patients, reviewers, nominators, decisionmakers, and policymakers. To improve the transparency and consistency of reporting, the workgroup recommended and integrated guidance into the updated topic refinement document (Appendix A):

- Detailed description of important and/or potentially controversial issues that arose during the topic refinement process.
- Summary of relevant points of the topic refinement team's discussion of controversial issues or issues that required balancing different viewpoints.
- Greater detail of rationales for revisions to the topic, including what changed, the timing, and information considered (i.e., literature scan, Key Informant input, topic refinement guiding principles).
- Inclusion of possible refinements that were considered, but did not result in a change.
- Inclusion of possible refinements that require additional future input (public commentary, Technical Expert Panel input, a more focused literature scan, etc.) or are otherwise more appropriate for the evidence review phase.
- Documentation of these changes in an easy-to-read tabular format.

Although the full topic refinement summary report is not posted publicly, the analytic framework, PICOTS, and Key Questions are posted for public comment (see next section). In addition, a high-level summary of input and changes are reported in the protocol during the systematic review stage.

Public Posting

In addition to Key Informant interviews, public posting offers an important means of capturing input from a broader sample of stakeholders. This also promotes transparency and stakeholder input, important aspects of the EHC Program. A document outlining the proposed scope (draft Key Questions, PICOTS, and analytic framework) is posted for public comment on the EHC Web site for 4 weeks (see Appendix A). The document also provides sufficient background to apprise the reader of the importance of the topic, uncertainties pertaining to clinical practice, potential impact on patient care, and the potential contribution of the proposed review. Any individual may comment; and commenters have included patients and other consumers, advocacy organizations, health care professionals, professional organizations, and industry representatives. Public comments may provide additional insights about the relative importance of outcomes and PICOTS elements to specific stakeholders, relevance of questions, additional relevant and interested stakeholders, clarity of wording, and potential approaches to frame the eventual evidence report.

Some individuals may attempt to answer the Key Questions rather than to comment on them. Nonetheless, such responses are still of value because they may point to relevant literature and guidelines, identify ongoing work by other organizations, highlight areas of low and high clinical uncertainty, provide insight into clinical or usual practice, and affirm the need for a new review. For example, for a recent review on inguinal hernia repair,[22] public input affirmed the importance and relevance of the topic and provided comments about certain procedures most commonly performed in the United States. This input affirmed that the review addressed the diversity of decisions and factors in inguinal repair, including surgical approach, fixation technique, mesh type, surgical experience, and setting. It also resulted in the elimination of two questions related to nonmesh procedures; expansion of questions related to three distinct populations; and reorganization of questions pertaining to mesh types and fixation methods.

At the end of the public comment period, the topic refinement and/or systematic review team reviews all comments. Additional revisions are documented in the topic refinement summary report. The revised Key Questions, PICOTS, analytic framework, and general highlights of comments and responses are included in the systematic review protocol. These elements are considered final after input from the Technical Expert Panel during the conduct of the systematic review.

Conclusion

To date, EPCs have conducted approximately 100 topic refinements. These topics represent a broad and diverse range of health care issues, each with its own clinical dilemmas, technical questions, coverage implications and/or policy challenges. Although the EHC Program stipulates the phases and common elements of topic refinement that EPCs must include, various EPCs have approached aspects of topic refinement in both similar and different ways. This variation among EPCs provided an excellent opportunity to learn and consider the advantages and disadvantages of different approaches to topic refinement. Our work group has reviewed the approaches used by various EPCs. We critically assessed the topic refinement process, and identified lessons learned. We have developed a set of guiding principles and identified practical approaches to conducting a topic refinement. The points of our report are presented in Box 3. Through the review of topic refinement summary reports, we offer recommendations to improve the reporting and transparency of the topic refinement process. Given the variability between topics and topic refinement investigators, these recommendations are not meant to be prescriptive. Skilled investigators must inevitably apply judgment and discretion in refining topics. Therefore, we envision investigators using these principles for more systematic and explicit decisionmaking.

Box 3. Key points

- The **goal** of topic refinement is to produce a topic that addresses important health care questions and dilemmas; considers the priorities and values of relevant stakeholders; reflects the state of the science; and allows for application of systematic review research methods.
- The **guiding principles** are: fidelity to the original nomination, relevance, research feasibility, responsiveness to stakeholder input, reduction of potential investigator bias, transparency, suitable scope.
    - These principles are consistent with EPC program topic selection criteria for systematic reviews and the principles for conducting systematic reviews.
- Variability of topics in the EPC program makes it impractical to apply the guiding principles in a prescriptive manner.
- Topic refinement is an iterative and phased process. The **stages** of topic refinement (Figure 2) are:
    - Initial topic refinement
    - Key Informant interviews
    - Public comment period
    - Synthesis and reporting
- **Initial topic refinement** gathers information from topical experts and a literature scan to develop the provisional PICOTS, analytic framework (AF), and Key Questions (KQs) of the topic to present to key informants for input.
- The **Key Informant** panel is comprised of 6 to 12 individuals. They reflect the perspectives of stakeholder groups who would make decisions with the findings of the report, as well as those affected by those decisions. Their input can improve the relevance and applicability of the systematic review.
    - To facilitate the recruitment process, a good practice is to make a prioritized list of more than one potential Key Informant for each category.
    - Commonly, 2-4 individuals are engaged at a time for interviews to allow for sufficient opportunity to express opinions and for interaction. Consensus is not a goal.
    - The team ensures that the group's mix of expertise and viewpoints are complementary.
    - Interviews are usually 60-90 minutes in duration, and conducted over 3 to 4 weeks.
    - The interviews are generally facilitated by a core member of the topic refinement team, with part or all of the topic refinement team in attendance.
- **Public comment** on the topic allows for input from a broader range of individuals.
- **Synthesis** of input requires judgment of the topic refinement team and consideration of the guiding principles. The investigators may balance certain principles when making decisions about whether and how to include comments from individual stakeholders or other sources of input, especially when they are conflicting. The topic refinement team is comprised of independent investigators; ultimately they are responsible for decisions about integration of input.
- In **reporting**, all decisions should be concisely and transparently documented in the topic refinement summary report. This report may be used by the topic refinement team, systematic review team, and AHRQ program officer to understand decisions made during topic refinement. It includes:
    - a summary of input (topical experts, literature scan, Key Informant, and public commentary)
    - important and/or critical issues that were raised
    - description of controversial or unresolved issues
    - changes in the PICOTS, KQs or AF, and the rationale in light of the guiding principles

While these recommendations can enhance and improve the process of topic refinement, our approach was limited in a number of ways. We were not able to assess the effect of topic refinement on the content of the systematic review, nor could we assess its effect on the uptake and presumed usefulness of the systematic review by stakeholders. While the opportunity existed to review public and peer review comments of the draft systematic reviews, the ability to make conclusions about the effect of topic refinement (or its elements) would be limited because of the input of other stakeholders during the systematic review process; other elements that affect perceived usefulness; and readability. While the topic refinement process is described as a linear process, oftentimes it is iterative and topic refinement summary reports may not reflect all considerations of investigators. The workgroup had a limited number of individuals from the EPC program, and thus a limited number of perspectives, but all workgroup members had experience in topic refinement across various EPCs, and the Project Officer had substantial

additional experience working with other EPCs. Additional insights from direct contact with other EPC investigators might have informed our results. However, we did receive critical input from EPC investigators representing all but one AHRQ EPC, and we revised the final report accordingly.

The EPC Program's current methods for topic refinement were developed and have iteratively evolved since 2007. In that time, investigators learned lessons about the relative strengths and limitations of various approaches and aspects of topic refinement. The recommendations in this report were developed from our work group's synthesis and assessment of approaches used by various EPCs to date. Questions still remain about many facets of the topic refinement process. How to most effectively identify and engage stakeholders? How to better understand the effects of the inherent subjectivity of the process and to modulate those effects when possible? We expect that methods will continue to evolve and that more will be learned about the best approaches to these and other challenges.

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Abbreviations

A1c/HbA1c	Hemoglobin A1c or glycated hemoglobin level
AHRQ	Agency for Healthcare Research and Quality
EHC	Effective Health Care
EPC	Evidence-based Practice Center
PICOTS	Population, intervention, comparator, outcome, timing, and setting
SRC	Scientific Resource Center

Glossary

AHRQ's Effective Health Care Program sponsors systematic reviews and the translation and dissemination of research findings to inform decisionmaking and improve the quality of health care services.

Evidence-based Practice Centers. EPCs are institutions in the United States and Canada contracted by AHRQ to develop systematic reviews and technology assessments on topics relevant to clinical and other health care organization and delivery issues. The EPCs also conduct research on methodology of systematic reviews.

Key Informants. This is a small number of stakeholders that provide input to the topic refinement team. They share their diverse perspectives and understanding of real-world context on specific topics during interviews facilitated by the topic refinement team. This in turn helps to inform the scope of the review, and improve the relevance and applicability of the results of the evidence review for decisionmakers.

Nominators. These are individuals that suggest topics for systematic review. He/she lends the topic initial direction and form by providing information about the questions, the affected population, the health-related benefits and harms.

Topic refinement team. This group is composed of investigators and other individuals with expertise in topic content, systematic review methodology, health care, facilitation, and stakeholder engagement.

Project Officer. This is an individual who represents AHRQ and serves as a point of contact to the Evidence-based Practice Center and its investigators. The Project Officer provides oversight to ensure consistency with the program processes, scientific methods, and principles.

Topical experts are individuals who have relevant content expertise and who are easily accessed by the topic refinement team. These may be clinicians or other health care providers, researchers, or other individuals who are well versed with the topic. These individuals provide input early in

the topic refinement process before Key Informant interviews. These interviews provide insight into technical issues, controversies, and the current state of knowledge about the topic.

Stakeholders are individuals or groups with an interest in the clinical decision and the evidence that supports that decision. These end users of research may be patients or caregivers, practicing clinicians, representatives of professional or consumer organizations, payers, policymakers, industry representatives, or others involved in health care decisionmaking. The EHC programs strives to include stakeholders in the research enterprise from the beginning to improve the end product and facilitate the diffusion and implementation of the findings. Involving relevant stakeholders also helps to ensure that the research reflects the various needs of all diverse users.

Appendix A. EPC Topic Refinement Document

Topic Refinement Content Guidance Document (Version 4 - 9/6/12)
Note: Topic Refinement Document is not for posting or public distribution.

This documents the stages of topic refinement. Each section is completed sequentially and submitted separately to AHRQ when completed. For further details about submission, please see the EPC Procedure Guide.

- **Part 1 is a record of activities and decisions from the beginning of topic refinement to the point just before Key Informant input.**
- **Part 2 includes the elements for public posting. This will be posted on the EHC website for four weeks for public comment.**
- **Part 3 documents activities and decisions from key informant engagement to up to public posting.**
- **Part 4 documents decisions in response to public posting.**

Part 1: Summary of Topic Development and Development of the Preliminary Scope (KQ, PICOTS and Analytic Framework)
Part 1 is completed and submitted to AHRQ prior to Key Informant discussions.

This documents scope changes and topic refinement activities (local expert input and preliminary literature scan) prior to key informant input. The preliminary key questions (KQ), PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Setting) and analytic framework (AF) are developed from the initial KQ and PICOTS with local expert input, Topic Triage considerations, and the preliminary literature scan.

Portions of this document are frequently used to inform key informant discussions. The background and historical detail about the topic nomination can provide context for the key informants; the KQ, PICOTS and AF outline the proposed scope of the topic; and the preliminary literature scan can inform discussion about relevant interventions, comparators, and outcomes, and other feasibility considerations.

Summary of Topic Development

	Fill in boxes with information from the Topic Triage Cover Sheet
Topic Name:	
Topic Number:	
Topic Triage Review Date:	
Topic Investigator(s):	
Nominator:	

Initial Key Questions from the Topic Triage Cover Sheet

Question 1
Question 2
Etc. with KQs

Initial PICO (Population, Intervention, Comparator, Outcome) from the Topic Triage Cover Sheet

P:	
I:	
C:	
O:	
Narrative:	

Considerations from Topic Triage Discussion

Summarize recommendations from the Topic Triage, such as scoping considerations and individuals to include as key informants. This information can be located in the Topic Triage Cover Sheet under "Summary of Discussion and Next Steps."

Development of the Preliminary Key Questions, Analytic Framework and PICOTS

Preliminary Key Questions

The Preliminary Key Questions are developed with input from local experts and with the Topic Triage recommendations in mind, and serve as the starting point for Key Informant (KI) discussions. These Preliminary Key Questions on the proposed topic should reflect important decisional dilemmas in health care for stakeholders. With this in mind, the Key Questions must clearly define the logic and scope of the topic. For further discussion of Key Questions, consult the Methods Guide and the EPC Training Modules.

Question 1:

a. Sub-Question 1
b. Sub-Question 1

Question 2:

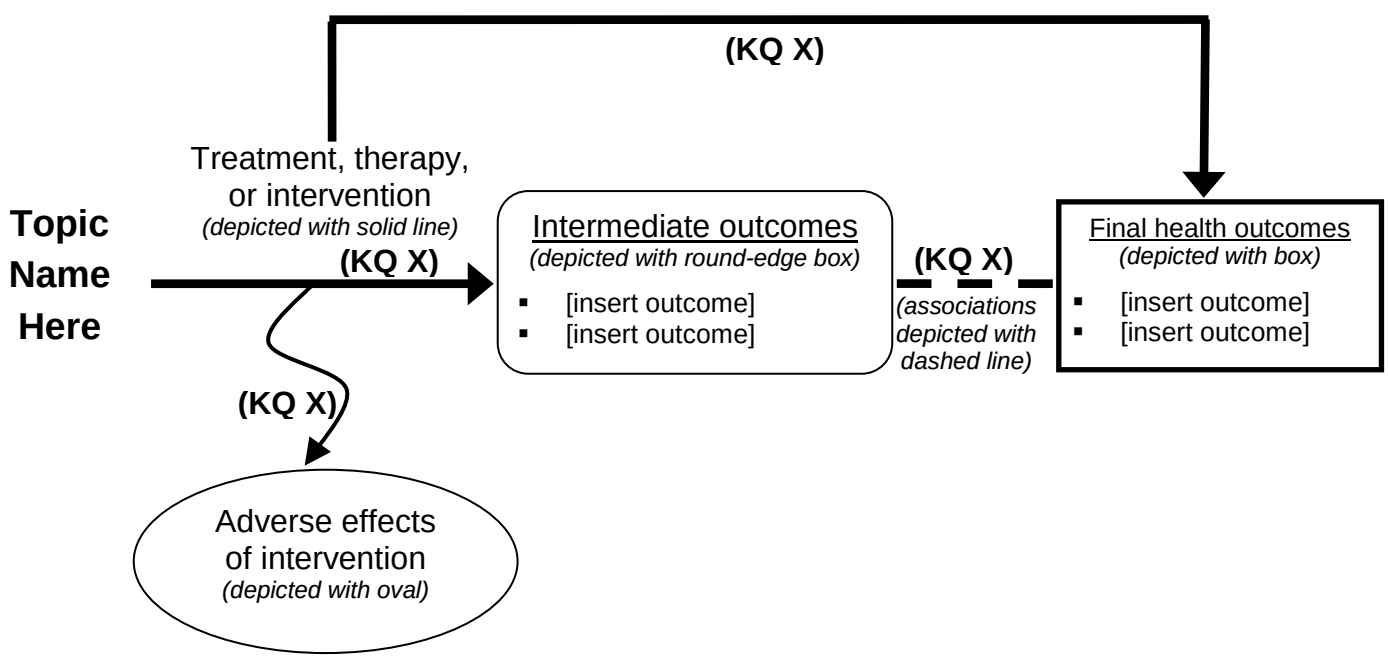
a. Sub-Question 2
b. Sub-Question 2

Etc. with Questions

Preliminary Analytic Framework

The Preliminary Analytic Framework provides a visual representation of the clinical logic and preliminary PICOTS (patients, interventions, comparators, harms, intermediate outcomes, and final health outcomes). The Preliminary Analytic Framework should be linked to the Preliminary Key Questions. For further details about analytic frameworks please see the Methods Guide and Training Modules.

Appendix Figure A1. Preliminary analytic framework for [insert title].



Preliminary Background

The Background section describes the condition(s), role of the intervention, relevant claims about comparative effectiveness and safety, and outlines the rationale for a systematic review on the topic. The background section will be a work in progress. This initial section developed for distribution to Key Informants should set the context for their discussion of the topic.

This will require a targeted literature scan by the EPC on the current state of the literature (see preliminary literature scan for specific details). If there is a large body of literature, the EPC will work with key informants to focus the questions on those most essential. The exact literature search and sources can be further refined after discussions with the Technical Experts during the review portion of the project.

Elements to include

- *Population:*
  - *Nature and burden of condition*
  - *Description of subpopulations, if appropriate*
- *Intervention, Comparator*
  - *Current treatment or standard of care and/or existing guidelines*
  - *Mechanism of action*
  - *Availability in the United States; FDA approval status*
  - *Are there interventions for which there is uncertainty regarding use?*
  - *Proposed advantages and disadvantages of the intervention (cost, invasiveness, harms, etc)*
- *Outcomes*
  - *What are the outcomes with the current standard of care?*
  - *What are the outcomes of importance for stakeholders?*
  - *What outcomes are studied in the literature?*
- *Setting and context*

- *Rationale for an evidence review*
    - *Controversy or uncertainty about a topic*
    - *Literature is confusing or conflicting*
    - *Relevant literature not in one place*
    - *Clinical decisions are complicated*
- *Relevance of research question to clinical decision making or policymaking*
    - *Theoretical and potential benefits or harms of the intervention or technology*
    - *Weighing benefits and harms*
    - *Targeting specific populations*
    - *Applicability to general practice (how will the review help readers understand how this intervention or technology fits with what is currently available?)*
    - *Patient preferences*
    - *Cost, if relevant*
    - *Coverage*
- *Availability of scientific data to support the systematic review and analysis*
    - *Studies*
    - *Systematic reviews*
- *Assessment of other ongoing work in this topic area.*
- *Other contextual factors (such as training, facility requirements, advocacy positions)*
- *Potential audiences of the proposed review. How will could this report be used (e.g., issues in guidelines, coverage decisions, or benefit design)?*

Preliminary PICOTS (patients, interventions, comparators, outcomes, timing, setting)

The PICOTS provide further detail of the key questions and analytic framework. Elements of the preliminary PICOTS should be consistent with the Preliminary Analytic Framework, and the TR team may choose to organize the sections of the PICOTS by key questions for greater clarity

Population(s)

- Insert, even if noted in KQs. The description will likely will include definitions or descriptions of population(s) named in KQs. e.g., "Adolescents" will include ages 13-19 years.
- *Specify by KQ if relevant.*

Interventions

- *Insert, even if noted in key questions or if just one intervention*
- *For medications, insert class of drug with a sublist of preparations by generic/chemical names.*
- *For devices, list type of device with relevant key features or characteristics.*
- *Include information on the FDA status, indications, and relevant warnings for drugs or devices to be included in the systematic review. This information may be included as an appendix.*
- *Specify co-interventions, if applicable*
- *Specify by KQ if relevant*

Comparators

- *Placebo or active control; usual care; other intervention*
- *Define if possible "usual care"*
- *Specify by KQ if relevant*

Outcomes

- *Specify by KQ if relevant*

Intermediate outcomes

1. [Insert]

Final health or patient-centered outcomes

1. [Insert]

Adverse effects of intervention(s)

1. [Insert]

Timing

- *Duration of follow-up*

Setting

- *Setting (primary, specialty, in-patient)*

Preliminary Literature Scan

Initial topic refinement requires a targeted literature scan on the current state of the literature (including guidelines, outcomes studied, scope of literature). This should not be synthesized. While the literature scan performed during topic development gives a general sense of the body of evidence, this search may be more specific, and provide greater detail about the topic and relative volume of literature. It can inform the Topic Refinement team about key areas to focus on in KI discussions, promote an informed discussion about potential debates and uncertainties related to the topic; guide formulation of the key questions; assist in identifying relevant interventions, comparators, and outcomes; and guide considerations in broadening or narrowing proposed scope. This can also identify additional literature and relevant SRs if a period of time has lapsed between the end of topic development and commencement of topic refinement activities.

If there is a large body of literature, the EPC will work with key informants to focus the questions on the outcomes, comparators and interventions that are most essential.

While limited evidence may be identified at this stage for particular KQ or portions of the topic scope, this does not necessarily preclude inclusion in the final review if it is an area that is of importance to decisionmakers and should be highlighted as an important gap in evidence. If there is a limited body of relevant literature identified for the overall proposed review or a recent relevant evidence review is identified, the EPC, with KI input, could consider whether the key questions could be focused differently or whether an evidence review on this topic would be possible or duplicative. After discussion with AHRQ, this may result in a decision not to proceed with the systematic review, or development of a different EPC product, such as a Technical Brief.

The exact literature search and sources will be further refined after discussions with the Technical Experts during the review portion of the project.

Elements to include

- *The databases searched*
- *Relevant guidelines*
- *Any recent relevant systematic reviews (to assess for any duplication)*
- *Types of interventions, comparators, and outcomes studied*
- *Types of intervention and comparator combinations that have been studied*
- *Areas of controversy or uncertainty identified*

Summary of Topical Expert Input

Topical experts provide input on current practice, available interventions, decisional dilemmas, etc. Often these individuals provide clinical context, and insight into the "real-world" situations of stakeholders. This should be a high-level summary of input from topical experts.

Table A1. Changes between initial KQ/PICOTS and preliminary KQ/PICOTS

Changes to the initial KQ and PICOTS may be informed by topical expert input, preliminary literature scan, or Topic Triage recommendation. This table provides documentation of issues or controversies, changes that were or were not made, and the rationale.

Original Element	Source	Comment	Decision	Change	Rationale
Intervention: nurse case management	Topical expert	Definition of nurse case manage-ment is too narrow	Broadened intervention to include case managers with training other than nursing	Case management, defined as the assignment of a single person, alone or in conjunction with a team, to coordinate all aspects of a patient's care	This will allow for a more thorough review of case management for adults with medical illness and complex care needs, while making it possible to compare different types of case management including that conducted by nurses. This broadens the relevance of the review to a larger audience.
Population: all patients	Literature scan	Literature scan identified diverse populations and variability in tasks of case manage-ment	Limited population to adults with medical illness, and exclude those for whom case management is used primarily to manage mental illness	Adults with medical illness and complex care needs	Limiting the scope to adults and medical illness would focus on a more homogeneous population and is more likely to provide usable information about the effective elements of case management.
KQ 1: In adults with medical illness and complex care needs, does case management * improve patient outcomes?	Topical expert, literature scan	Complex care needs seems overly broad and vague	No change	NA	We agree that this is a broad population, and have purposely kept the definition of "complex care needs" broad. From the literature scan, the studies appear to be heterogeneous with regard to the populations and interventions. We anticipate considerable variation in the basis upon which studies consider care needs to be complex. Given this heterogeneity, we believe that keeping the definition broad in this respect will prevent an overly narrow review that misses important approaches to case management. Our feasibility scan identified 26 RCTs/CCTs between 2006 and 2009 (after the Stanford-UCSF report) that **may be** applicable to the topic. This scan was not restricted to adults or medical illness. Despite the diversity of the studies identified in this scan, this would seem to be an encouraging sign that the relevant body of literature is manageable for this review.

Considerations for Key Informants (KI)

This section outlines specific questions and issues to focus and structure the discussion with KI. The KI panel may clarify elements of the Preliminary Key Questions, Analytic Framework, and PICOTS. They may also provide insight into issues that have been inadequately captured in the limited literature search and local expert input, or because specific issues require the perspective, experience, or technical knowledge of the KI panel. KI input should help the TR team to understand the questions that decision-makers struggle with (decisional dilemmas) to ensure the review addresses these issues. They may also identify relevant interventions and outcomes that are most important for decisionmaking, and identify current standards of care to inform the TR team about the most appropriate comparators to include in the evidence review.

Input will be solicited from a KI panel comprised of a small number of individuals. Relevant individuals may be patients and consumers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others who will use the findings from the report to make healthcare decisions for themselves or others. The KI panel should include perspectives of individuals who would make decisions with the findings of the report, as well as those who would be affected by these decisions. These informants are distinct from the Technical Expert Panel which is constituted to inform the scientific processes of the evidence review.

Potential issues to address with key informants:

- *Standard of care, to inform relevant comparators*
    - *What is the current perception or understanding of guidelines or standards of care?*
    - *How is usual care defined?*
- *Relevant interventions*
    - *What interventions or technologies are you currently using?*
    - *How widespread is the use of the interventions or technologies?*
- *Uncertainty, decisional dilemma*
    - *Is there variability in clinical practice? Is this a problem?*
    - *Do the questions capture this adequately?*
    - *Outcomes (benefits and harms). What is your current understanding of outcomes with the current standard of care? (or if no current treatments are available, what is your understanding of the natural progression of disease?)*
    - *What are the potential advantages or disadvantages of one intervention or technology over others? (i.e. ease of use, access, cost, invasiveness, patient preference, use of other resources or tests)*
    - *Why might you be interested in this intervention or technology?*
    - *What would keep you from using it?*
    - *Is it important to know how well an intervention works? Or just that it works?*
    - *What benefits or harms (outcomes) would influence whether you would use or recommend this intervention or technology?*
    - *What outcomes are most important for you to make a decision? Which outcomes are less important?*
- *Contextual issues*
    - *Are there other considerations which influence decisions about care?*
    - *Are there certain settings or populations which should be included or specifically studied?*
    - *Are there other considerations in decisionmaking that are important, such as insurance coverage, geography, etc.?*
- *Targeted questions regarding PICOS or other elements of the proposed scope*

Questions and issues for Key Informants

1.	
2.	
3.	
4.	
5.	
6.	

Part 2: Key Question Posting Document for [*Insert Title*]

Draft Key Questions

Question 1

c. Sub-Question 1

d. Sub-Question 1

Question 2

e. Sub-Question 2

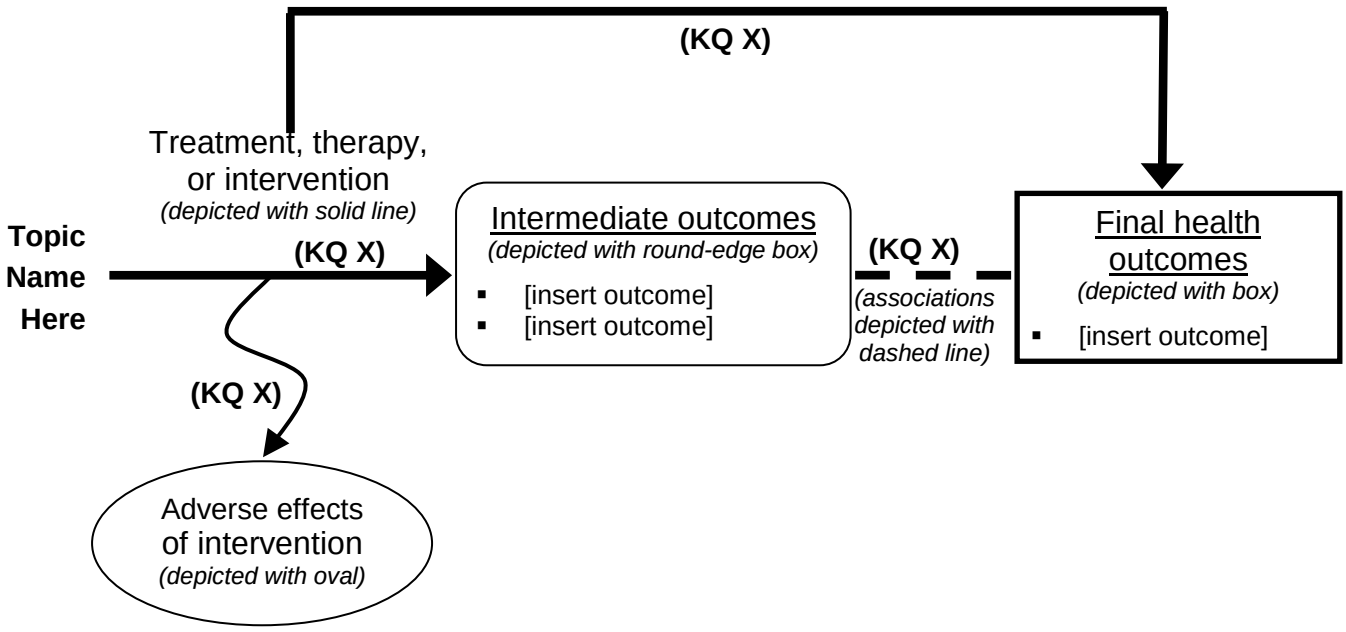
f. Sub-Question 2

Etc. with Questions

For updates of reports specify if changes have been made to the original key questions and provide some discussion of the changes.

Draft Analytic Framework

Appendix Figure A2. Draft analytic framework for [*insert title here*].



Include alternate text to accompany the figure (for 508 compliance) ***in a separate file****. For example:*

Appendix Figure A2: This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how [treatment 1] versus [treatment 2] may result in intermediate outcomes such as A, B or C and/or long-term outcomes such as X, Y or Z. Also, adverse events may occur at any point after the treatment is received.

Background (2-5 pages)

The purpose of the Background section is to describe the condition(s), role of the intervention, relevant claims about comparative effectiveness and safety, outline the rationale for a systematic review on the topic, and describe expected audience. Please see specific elements for inclusion in "Preliminary Background", Part 1 of the Topic Refinement Document.

It is expected that the background section will be revised in response to key informant input and elements of the targeted literature scan. It may also be revised to provide more specific and relevant context for the draft key questions, PICOTS and analytic framework.

Population(s)

- *Insert, even if noted in KQs. The description will likely include definitions or descriptions of population(s) named in KQs. e.g., "Adolescents" will include ages 13-19 years.*
- *Specify by KQ if relevant.*

Interventions

- *Insert, even if noted in key questions or if just one intervention so potential sources of Scientific Information Packets are apparent to the public.*
- *For medications, insert class of drug with a sublist of preparations by generic/chemical names.*
- *For devices, list type of device with relevant key features or characteristics.*
- *Include information on the FDA status, indications, and relevant warnings for drugs or devices to be included in the systematic review. This information may be included as an appendix.*
- *Specify co-interventions, if applicable.*
- *Specify by KQ if relevant.*

Comparators

- *Placebo or active control; usual care; other intervention.*
- *Define if possible "usual care."*
- *Specify by KQ if relevant.*

Outcomes

- *Specify by KQ if relevant.*

Intermediate outcomes

1. [Insert]

Final health outcomes

1. [Insert]

Adverse effects of intervention(s)

1. [Insert]

Timing

- *Duration of follow-up*
- *Specify by KQ if relevant*

Setting

- *Setting (primary, specialty, in-patient)*
- *Specify by KQ if relevant*

Definition of Terms

References

Appendix A References

1. Kemper A, Coeytaux R, Sanders G, et al. Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA). Comparative Effectiveness Review No. 28. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290 2007 10066-I.) AHRQ Publication No. 11-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Appendix B. Example of Selected Aspects of a Topic Refinement

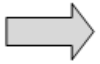
Appendix Figure B1. Nomination: The effectiveness of disease-modifying anti-rheumatic drugs in children with juvenile idiopathic arthritis[1]

Nominated PICO

Population: Children and subgroups of children diagnosed with JIA
Intervention: Corticosteroids; Synthetic DMARDs; Biologic DMARDs
Comparator: Comparisons of different DMARDs
Outcome: Outcomes include looking at potential harms and benefits of various treatments.

Nominated Key Question

For children with juvenile idiopathic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (feeling healthy, not experiencing pain, functioning well, and not having flare-ups)?



Refined PICO

Population: Children and subgroups of children diagnosed with JIA
Intervention: Various DMARDs
Comparator: Placebo, NSAIDs and/or corticosteroids, or other DMARDs
Outcome: Patient-centered outcomes (such as pain control, clinical remission, and quality of life); intermediate outcomes (laboratory measure of inflammation, number of joints with limited range of motion); and adverse effects of treatment.

Refined Key Questions

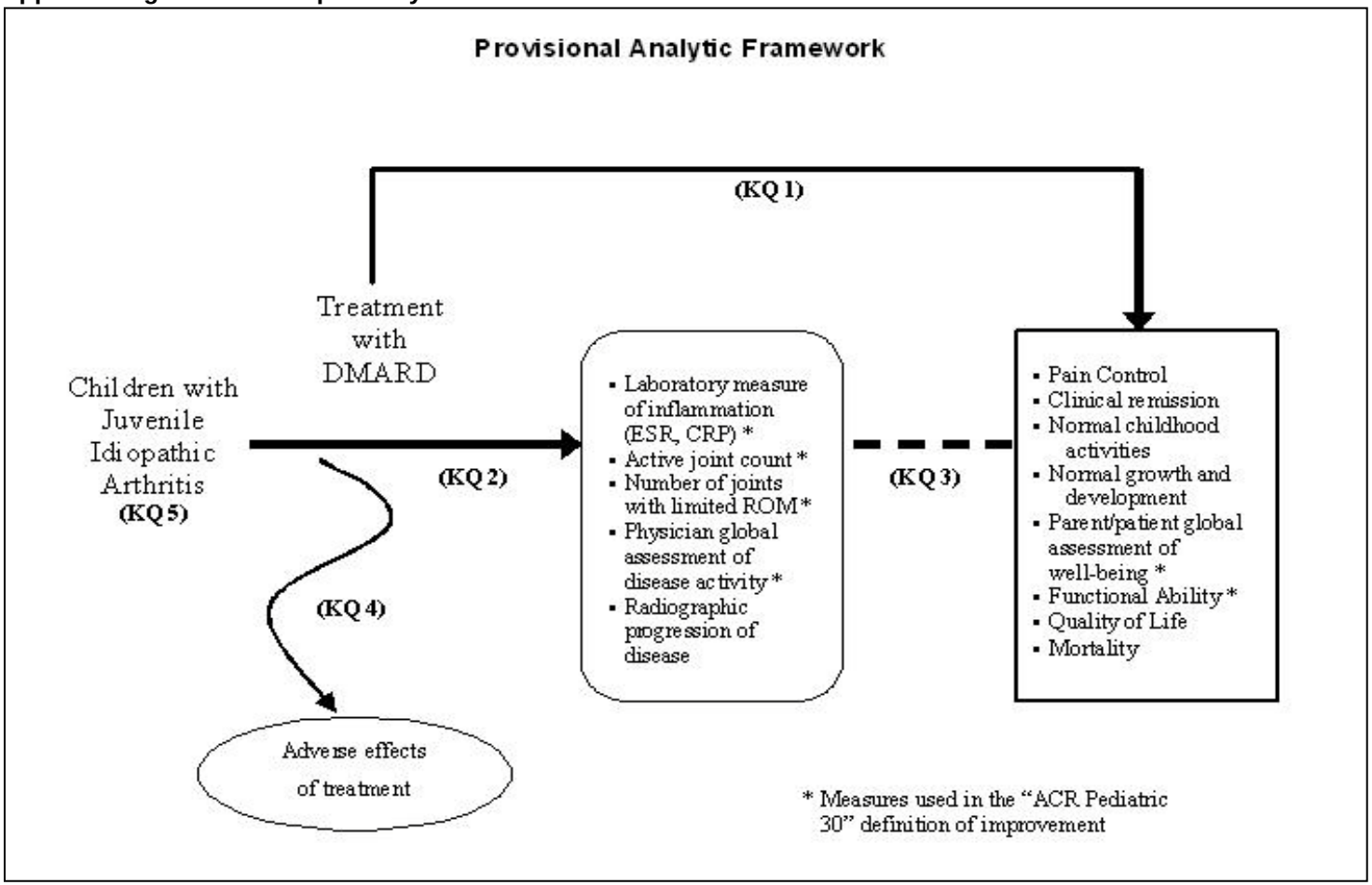
In children with JIA
KQ1: Does treatment with any of a variety of DMARDs, alone or in combination, improve health outcomes (i.e. pain control; clinical remission; quality of life; parent/patient global assessment; mortality; function; or growth and development) compared with placebo, NSAIDs and/or corticosteroids, or other DMARDs?
KQ2: Does treatment with any of a variety of DMARDs, alone or in combination, improve other outcomes (i.e. active joint count; number of joints with limited ROM; laboratory measures of inflammation; physician global assessment; or radiographic change) compared with placebo, NSAIDs and/or corticosteroids, or other DMARDs?
KQ3: Is improvement with other outcomes associated with improvement in health outcomes?
KQ4: Does treatment with any of a variety of DMARDs, alone or in combination, result in additional troublesome or serious harms compared with placebo, NSAIDs and/or corticosteroids, or other DMARDs?
KQ5: How do the efficacy, effectiveness, safety or adverse effects of treatment with DMARDs differ between each of the various subtypes of JIA?

Note: DMARD= disease-modifying anti-rheumatic drug, JIA=juvenile idiopathic arthritis, KQ=key question, NSAID=nonsteroidal anti-inflammatory drug, PICO=population, intervention, comparator, outcome.

Appendix Table B1. Changes to elements of the nominated topic with rationale for refinements

Original Element	Source of Input	Comment	Decision	Change	Rationale
Nominated KQ	Local expert, literature scan	There are at least six sub-types of JIA, with distinct clinical characteristics and different treatment approaches. The amount of published literature for each subtype varies substantially.	Specify in the KQ that subtypes of JIA exist and that the population of interest will include children with any subtype.	-No change in PICO. -KQ 3 was added about possible variations in effectiveness and safety of DMARDs between subtypes.	Added detail about subtypes makes the key questions more specific, and improves the accuracy and research feasibility of the SR. Inclusion and analysis by JIA subtypes might expand the scope and heterogeneity of the SR; however the literature predominately addresses two subtypes and reduces this concern.
PICO (Intervention): Corticosteroids; Synthetic disease-modifying anti-rheumatic drugs (DMARDs); Biologic DMARDs	Literature scan, Key Informant	Corticosteroids are commonly used as first-line treatment for most cases of JIA.	Remove as a intervention, and include as a comparator	Intervention: DMARDs	This change reflects the standard of care and the literature. This does not significantly compromise fidelity to the original nomination. The principal dilemma relates to DMARDs and not corticosteroids; this makes them better suited as a comparator for DMARDs.
PICO (Outcome): Outcomes include looking at potential harms and benefits of various treatments	Literature scan, Key Informants, Local Experts	Specific outcomes are not included	Include relevant outcomes, and specify them in the key questions and PICO	-See refined KQs -Outcome: Patient-centered outcomes (such as pain control, clinical remission, and quality of life); intermediate outcomes (laboratory measure of inflammation, number of joints with limited range of motion); and adverse effects of treatment.	Distinguishing between patient-centered outcomes and intermediate outcomes elucidates the underlying relationship of the outcomes and the logic of the SR
Nominated KQ	Literature scan, key informant, local experts	The outcomes listed do not reflect the clinical logic typically seen in AFs and refined KQs. The nominated topic places patient-centered outcomes (e.g., patient functioning) and intermediate outcomes (e.g., radiographic joint damage) in the same key question.	Formulate key questions specific to the outcome categories (patient-centered outcome; intermediate outcome).	-KQ: See refined KQ 1 (patient-centered outcomes) and KQ 2 (intermediate outcomes). -AF: The relationship of the outcome categories is represented in the AF	Accuracy and research feasibility are improved by including specific outcomes in the KQ. Distinguishing patient-centered outcomes from intermediate outcomes elucidates the underlying relationship of the outcomes and the logic of the SR.
Nominated KQ	Literature scan	Many studies use ACR Pediatric 30, a validated composite measure of improvement of JIA. It includes patient –centered outcomes and intermediate measures. Some measures of the Peds 30 were included in the nominated materials.	Include mention of Peds 30 measure in the AF.	In the AF, asterisks (*) have been added to the outcomes that are constituents of the Peds 30 measure.	The literature scan provided added detail about relevant outcomes, including that part of the ACR Pediatric 30. This improves the accuracy and research feasibility of the review.

Appendix Figure B2. Example analytic framework



Note: CRP=C-reactive protein, DMARD= disease-modifying anti-rheumatic drug, ESR = erythrocyte sedimentation rate, KQ = key question, ROM=.range of motion

Key Questions

KQ1: Does treatment with any of a variety of disease-modifying anti-rheumatic drugs (DMARDs), alone or in combination, improve health outcomes (i.e. pain control; clinical remission; quality of life; parent/patient global assessment; mortality; function; or growth and development) compared with placebo, NSAIDs and/or corticosteroids, or other DMARDs?

KQ2: Does treatment with any of a variety of DMARDs, alone or in combination, improve other outcomes (i.e. active joint count; number of joints with limited ROM; laboratory measures of inflammation; physician global assessment; or radiographic change) compared with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, or other DMARDs?

KQ3: Is improvement with other outcomes associated with improvement in health outcomes?

KQ4: Does treatment with any of a variety of DMARDs, alone or in combination, result in additional troublesome or serious harms compared with placebo, NSAIDs and/or corticosteroids, or other DMARDs?

KQ5: How do the efficacy, effectiveness, safety or adverse effects of treatment with DMARDs differ between each of the various subtypes of juvenile idiopathic arthritis (JIA)?