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

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Preface

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

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

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

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

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The Refinement of Topics for Systematic Reviews: Lessons and Recommendations from the Effective Healthcare Program

Structured Abstract

Objective. 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. Topics for reviews conducted through this program are nominated by a variety of stakeholders. Before reviews commence, nominated topics undergo a refinement process to ensure that the key questions are relevant, researchable, and of appropriate scope. Working through the EHC Program, Evidence-based Practice Centers (EPCs) have approached the topic refinement process in similar and different ways. AHRQ convened a work group to synthesize and assess current approaches to topic refinement and to develop recommendations for effective practices; we report our findings here.

Design and Setting. We formed a work group consisting of four investigators from four EPCs in the United States and Canada and one project officer from AHRQ. All participants held experience in topic refinement. We generated a prioritized list of methodological questions and possible guiding principles to be considered in the topic refinement process. We discussed each issue until we reached agreement on recommendations.

Results. The topic refinement process requires the topic refinement team to judiciously balance a variety of practical principles. Considerations include fidelity to the original nominated topic, public health and/or clinical relevance, researchability, transparency, scope, possible investigator bias, and responsiveness to stakeholder input. The relevance and application of these principles will vary by topic. Here we discuss the implications of each principle and issues to consider when applying them. We also describe the mechanics and logistics of the topic refinement process. Finally, we share our recommendations on the use of a literature scan, developing key questions and analytic frameworks, consulting topical experts, engaging stakeholders, and incorporating stakeholder input.

Conclusion. Systematic reviews that are accurate, methodologically rigorous, and as relevant and useful as possible for stakeholders require that topics be well refined and that key questions be well considered and well formed. 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.

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Introduction and Background

“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, clinicians, agencies that issue guidelines, policymakers, industry, or health care organizations.

To provide useful answers, systematic reviews must ask the right questions. Challenges arise when stakeholder-nominated topics are not optimally formulated for the broadest public health and/or clinical relevance or for researchability using accepted methods. Additionally, nominations might not optimally 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.

Formulating the right key questions to be addressed by a systematic review requires technical knowledge of the health care topic of interest, expertise in the methods of systematic review research, sufficient familiarity with the relevant literature, and an understanding of the values and priorities of relevant stakeholders. Before reviews are conducted through the EPC Program, nominated topics undergo a refinement process. This process aims to ensure that key questions are relevant, researchable, and of appropriate scope. Topic refinement involves a literature scan, input from topical experts, development and formulation of key questions and an analytic framework, engagement of and elicitation of input from stakeholders, and incorporation of that input into the refined topic. The practical principles and considerations that govern the topic refinement process include fidelity to the original nominated topic, public health and/or clinical relevance, researchability, transparency, scope of the topic, possible investigator bias, and responsiveness to stakeholder input.

Systematic reviews that are more accurate, methodologically rigorous, and as relevant and useful as possible for stakeholders require that topics that be well refined and that key questions be well considered and well formed. EPCs have approached the process of topic refinement in 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 recommendations for best effective practice. This report details guiding principles and methodological recommendations that may help investigators to effectively refine topics for systematic reviews, both within and outside of the EPC Program.

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 (who assess each topic for its suitability to the EPC Program before refinement). We use the term “provisional” to refer to the elements of the “initial topic refinement phase” (described below). These “provisional” elements are: (1) descriptions of the populations, interventions, and outcomes 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 local experts. These elements are considered provisional because they still do not include the input of multiple 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).

Topic Refinement in the Evidence-based Practice Center Program

AHRQ’s EPC Program conducts systematic reviews on health care topics to address the needs of a broad range of stakeholders in the design, organization, and delivery of health care. Topics may be nominated for review by stakeholders, who may include patients, clinicians, researchers, and agencies that issue guidelines, policymakers, and representatives of 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, a rarity in the traditional academic model. Collaboration of this sort reflects the broader social and public relevance of health care research.

As noted, original topic nominations may not optimally reflect the topic’s relevance to public health or clinical practice, or the current state of the science related to the topic. Additionally, nominations may not be sufficiently well formulated to be practically researchable. To ensure that systematic reviews provide the most useful answers, the EPC Program developed a topic refinement process for producing key questions and analytic frameworks that are both optimally relevant and researchable. Topic refinement occurs after the initial process of selecting nominated topics for inclusion in the EPC program. A team of investigators reviews topic nominations and determines which ones to recommend for refinement and systematic review. These recommendations are based on EPC Program principles, priority conditions, and selection criteria.⁵ Selected topics then undergo the topic refinement process addressed in this report.

The Topic Refinement Template: A Process Guide

The Scientific Resource Center (SRC), currently housed at the Oregon EPC, provides scientific and technical support for the EHC Program. Beginning in 2007, the SRC and AHRQ investigators and staff members collaboratively developed methods for topic refinement. Through conducting numerous topic refinements, investigators and staff members gained valuable knowledge and insights that they then integrated into the process. Thus, topic refinement methods were iteratively modified and eventually formalized into a “Topic Refinement Template” (see Appendix A). Since 2009, the EPC program has used this working document as a guide to a systematic topic refinement process and as a template for drafting the

topic refinement summary reports that are associated with individual topic refinements. Now with continued experience the EPC program is revising the Topic Refinement Template.

The current topic refinement process involves two main phases. The initial topic refinement phase involves collecting and preparing background information, provisional key questions, a provisional analytic framework, and considerations for interviews with Key Informants representing various stakeholder groups. The background section of a topic refinement summary report summarizes the nomination and the clinical and scientific context of the topic. To draft the background section, the research team conducts a targeted literature search and may consult a topical expert. The background should describe controversies or uncertainties about the topic, the relevance of the question to clinical decisionmaking and/or policymaking, and the availability of scientific evidence to support the systematic review. The key questions and analytic framework are formulated around specified populations, interventions, comparators, outcomes, timing, and settings (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. Finally, the investigators formulate a set of considerations to guide and structure discussions with key stakeholder informants.

During the second phase of topic refinement, the topic refinement team conducts interviews with the key stakeholder informants. Through these interviews, the team elicits input on issues not otherwise resolvable with a limited literature search and/or issues 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 completing refinement.

Objectives of the Topic Refinement Work Group

Using the EPC Topic Refinement Template as a guide, AHRQ's EPCs have produced summary reports of the refinement of approximately 100 topics for systematic reviews. The Topic Refinement Template stipulates the required phases and common elements of topic refinement, as described above. Nonetheless, EPCs have approached specific aspects of topic refinement in both similar and different ways. As mentioned, this variation offered an opportunity to identify the advantages and disadvantages of different approaches to aspects of topic refinement. To that end, AHRQ convened a work group to assess the topic refinement process and develop recommendations for effective approaches.

The objectives of the topic refinement work group were: (1) to review and synthesize the approaches to topic refinement used by various EPCs; (2) to critically assess all aspects of the topic refinement process; (3) to identify lessons learned by various EPCs related to both successful and unsuccessful strategies in topic refinement; (4) to articulate a set of guiding principles for the topic refinement process; and (5) to describe a set of effective approaches to consider when conducting a topic refinement. Although the work group addressed these objectives as they relate to the EHC Program, we also expressly considered the general relevance of the principles and practices.

Methods

We convened a work group consisting of four investigators from four 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 project manager for a topic refinement team provided input on the logistics and management of the process.

Investigators each presented a description of their own EPC's approach to topic refinement, including routine procedures as well as perceived strengths, challenges, and problems with the approach. In this way, group members gained familiarity with each other's procedures, identifying shared practices as well as unique aspects of each EPC's topic refinement process. Investigators then individually reviewed three topic refinement summary reports previously produced by EPCs other than their own. We compared the topic refinement summaries to elucidate: (1) similarities and differences in the elements of the original PICOTS and key questions that were refined, (2) the rationales used in making refinements, (3) the 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 reports; and/or (3) especially variable between EPCs. The list included items related to the overall purpose of topic refinement, the goals of particular aspects of topic refinement (e.g., the engagement of stakeholders), the relationship of topic refinement to the CER process, the roles and responsibilities of various participants, general principles to apply, and practical procedures to follow. We generated an initial list of 33 items, which were consolidated according to common themes into a final list of 17 items for the work group to discuss. We report the outcomes of these discussions in the results section of this report.

To structure our tasks, each group member ranked the final 17 items by order of priority for consideration. A combined prioritized list was generated based on these individual rankings. We discussed each of these items during twelve 90-minute teleconference meetings over 6 months. All meetings were audio recorded, and detailed minutes of the meetings were reviewed and discussed by all group members. We strove to assess critically the factors related to 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 for topic refinement. Recognizing that different topics inherently vary in their requirements for refinement, we did not seek to develop uniform recommendations for practical procedures. Rather, we sought to articulate viable approaches to realizing the goals of topic refinement and to describe the relative advantages and disadvantages of each approach.

Results

What is Refinement?

The concept of refinement may include the removal of unneeded elements, as in the refinement of mineral ores by removing impurities. It may also refer more generally to improvement in quality or purity. Refinement implies making changes to attain a better fit with a certain standard. In this latter 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 should accurately and precisely reflect the health care question or dilemma the systematic review is intended to address. It should align with the priorities and values of the most possible 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. Categories of 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**

As noted in the Introduction, 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 optimal public health and/or clinical relevance and for researchability may involve narrowing the focus of some elements of the PICOTS, expanding some elements, or a combination of both. This process more closely resembles sculpting in clay than sculpting in marble.

Topic refinement investigators should 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 optimally relevant and researchable (and therefore useful) key questions lie at the heart of the topic refinement process.

The Roles of Various Contributors in Topic Refinement

The topic refinement process begins with questions limited to a particular stakeholder's perspective. The topic refinement team then gathers and synthesizes input from a variety of sources in an unbiased, systematic, and transparent manner to produce a topic that is relevant for decisionmaking for a variety of stakeholders. To that end, each participant in topic refinement plays a unique and important role.

1. AHRQ's Effective Health Care Program sponsors new research, systematic reviews, and the translation and dissemination of research findings to a variety of audiences, including clinicians, consumers, and policymakers. Information from AHRQ-sponsored research supports informed decisionmaking and improves the quality of health care services. The EHC Program aims to address the needs (applicability, relevance, value) of a broad range of stakeholders in the design, organization, and delivery of health care. This approach reflects the broader social and public relevance of health care research.
2. The Task Order Officer represents AHRQ and interfaces with the EPC through the lifetime of the topic in the program. The task order officer provides Agency oversight, ensures consistency with EPC processes and methods, and ensures that the developing review remains consistent with EHC topic selection criteria (appropriateness, importance, potential for redundancy/ feasibility, potential value) and EHC Program principles (transparency, attention to subgroups and priority populations, involvement of stakeholders, and relevance). Established EPC processes promote a scientifically rigorous, systematic, unbiased, and consistent approach to systematic review; EPC methods promote the use of rigorous and consistent scientific methods.
3. EPCs are institutions in the United States and Canada contracted by AHRQ to develop evidence reports and technology assessments on topics relevant to clinical and other health care organization and delivery issues. Evidence reports may be used to inform and develop coverage decisions, quality measures, educational materials and tools, guidelines, and research agendas. The EPCs also conduct research on methodology of systematic reviews. Each EPC is staffed with researchers who represent a broad range of scientific backgrounds including medicine, pharmacy, systematic review, biostatistics, public health, and library science. Consistent with AHRQ's conflict of interest policies, EPC researchers have no vested interest in particular treatments or outcomes of an assigned evidence review topic.
4. The topic refinement team is composed of investigators and other individuals from an EPC with expertise in topic content, systematic review methodology, healthcare, facilitation, and stakeholder engagement. They are specifically concerned with the refinement of health care topics to be addressed by systematic reviews of literature. This team elicits input from stakeholders and local experts and performs the initial literature scan, using a systematic and consistent approach. They carefully weigh these inputs, balance stakeholder perspectives, and mold a topic scope that will yield an evidence review that will be feasible, relevant for a variety of stakeholders, and useful for decisionmaking.
5. The systematic review team composition may be similar to and even overlap that of the topic refinement team. Expertise represented includes content or topic knowledge, systematic review methodology, library science, and biostatistics. This team develops the evidence review protocol based on the scope from topic refinement with input from a

technical expert panel. The systematic review team develops the review consistent with EPC program processes and systematic review methods. The evidence report includes a systematic and comprehensive literature search for studies; transparent documentation of the assessment of the validity of the findings; a thoughtful evidence synthesis to answer key questions in the protocol; identification of evidence gaps; and recommendations for future research.

6. Local experts are individuals who have relevant topical expertise and who can be easily accessed by the topic refinement team. These may be clinicians or other healthcare providers, researchers, or other individuals who are well versed with the topic. They are engaged early in the topic refinement process to provide informal input on the initial scope, the current state of the science of the topic field, clinical or decisionmaking uncertainty, current practice, and relevant contextual issues. With this input the topic refinement team formulates the preliminary key questions, PICOTS, and analytic framework to be presented to the Key Informant panel.
7. Stakeholders are individuals or groups with a vested 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. Stakeholder participation in research can improve the relevance of the final product for a variety of decisionmakers and improve applicability to real-world situations. Engaged stakeholders also help to diffuse and implement research findings. This inclusion of stakeholders and end users of research in the process of asking and answering questions about health care rarely occurs with the traditional “ivory tower” approach.

Key Informants are individuals who represent a particular stakeholder group. Invited Key Informants comprise a panel representing diverse perspectives from larger stakeholder groups. Key Informant panels are typically comprised of 6 to 12 individuals, and may include the original topic nominator. The perspectives represented in the panel vary by topic. Key Informants provide input to the topic refinement team to improve the relevance and applicability of the proposed evidence review for decisionmakers. The type of input may relate to the relevance of the proposed key questions, the outcomes most important for decisionmaking, relevant populations, currently used interventions, current clinical practice or uncertainty, or relevant guidelines or literature.

8. Nominators are individuals or organizations that nominate topics for systematic review. Consistent with EHC Program principles, all stakeholders are invited to nominate topics. The nominator has a specific perspective and, often, specific reasons for nominating the topic. He/she lends the topic initial direction and form by providing information about the proposed questions, the affected population, the health-related benefits and harms, as well as the topic’s fit with the EHC Program criteria. The nominator may be interested in developing a clinical practice guideline or recommendation based on the evidence review, and may provide additional input as a Key Informant during topic refinement. Original nominations vary in their completeness and focus. The nominator may first give input during topic development when AHRQ determines appropriateness for systematic review (according to EHC topic selection criteria). The nominator may remain engaged in the process of topic refinement, providing more specific detail about the original topic nomination.

Guiding Principles

In refining a topic, investigators must make numerous decisions to include, exclude, or otherwise modify aspects of the populations, interventions, comparators and outcomes of interest. They must also decide how these elements of the PICOTS should relate to one another as formulated in the key questions and analytic framework. The principles that may guide these decisions include maintaining fidelity to the original nomination; improving the topic's relevance for particular populations or outcomes; assuring that the scope yields a coherent topic that fits within the EPC program; and defining the topic in a way that allows it to be effectively researched.

Although this report aims to describe effective practices and approaches to topic refinement, the great variability between topics makes it impractical to apply a standardized set of recommendations in a uniform manner. The importance of each factor or principle may vary according to the topic being refined. If a nominated topic is broad and multifaceted, then considerations related to the scope of the topic might be essential. If a nominated topic specifies an outcome pertaining to a limited group of patients or potential circumstances, then the topic refinement team may especially need to consider the relevance of the topic. If technical or clinical aspects of the topic indicate the need for certain modifications, then fidelity to the original nomination may be less important. If a topic was nominated for a specific purpose, such as to inform the development of guidelines, then responsiveness to certain stakeholders may be especially important. Such considerations are at the root of topic refinement.

The refinement of any topic usually requires consideration of numerous factors and the modification of multiple elements of the original nomination. This deliberative process involves thoughtful balancing of the relevant factors, often with trade-offs between various objectives. Our reviews of previous topic refinements suggest that each investigator considers and applies different principles when making decisions and refinements; however, the basis upon which these decisions should be made has not been previously formalized. We propose herein the following set of basic guiding principles that should be routinely and systematically considered in the course of refining a nominated topic for a systematic review. We recognize that one of these, "Scope," is distinct from the other principles, in that a description of the optimal scope of the topic is a *goal* of topic refinement and not a principle, per se. However, in practice considerations of scope—too narrow or too broad—and its implications are often applied to topic refinement decisions in much the same way as the other principles.

We do not prescribe *how* these principles should be applied or balanced for individual topics, only that they *be* considered. Inevitably, skilled investigators will have to use their judgment and discretion in refining topics. We envision investigators using these practical principles for more systematic and explicit decisionmaking. This in turn will make for a thorough and rigorous process producing results that optimally meet the criteria of a well-refined topic (Box 1).

Fidelity to the Original Nomination

Although the EHC program does not strive specifically to satisfy the nominator, fidelity to the original nomination is one of the major guiding principles of topic refinement. Fidelity to the original nomination is respectful to both the nominator and the intent of the nomination process. Much scientific research serves the academic purpose of generating new scientific knowledge, without input from external stakeholders or end users of research products. One guiding principle that distinguishes EHC Program it opens the opportunity to nominate topics and participate in the

research process to a broad range of stakeholders—from patients to advocacy groups to professional societies. This open process brings topics that may be important but previously unknown to researchers to the attention of the EHC Program.

Topics as originally nominated may not be “research ready,” and may require extensive refinement and development. However, the idea of topic refinement is not to develop an entirely new set of PICOTS. Rather, it is to refine the nominated topic by enhancing the researchability and relevance of the key questions and topic scope. The resultant product should then be useful to the original nominator as well as the broadest possible range of stakeholders. Thus, while the topic scope may need to be broadened (to be relevant to a larger audience), or narrowed (to be practically researchable), the topic refinement team should continuously refer to the originally nominated topic to ensure that their end product retains the spirit and intent of the nominator. The principle of “fidelity to the nomination” guarantees that the systematic review will have relevance to a ready audience (discussed below).

Relevance

Relevance is a guiding principle closely tied to fidelity to the original nomination. The EHC Program was created to provide research and information to clinicians, consumers, and policymakers by compiling, synthesizing, and translating evidence into useful formats for a wide range of audiences.⁶ In addition to soliciting input from stakeholders, the EHC Program attempts to align research priorities for maximum utility to a real-world audience. This idea underlies the guiding principle of relevance. Topics should be relevant to decisional issues that matter to the audience of review users.

However, even when nominated topics are of high relevance to the nominator, they may be too narrowly framed to be of significant use to a broader audience. Thus, topic refinement researchers may broaden or change the scope of the topic to increase relevance to a broader audience. Alternatively, the topic as originally nominated and scoped may be overly broad or duplicative with existing research. In this case, the topic refinement team may wish to narrow the scope of the review to sharpen its focus. Topic refinement involves balancing the tension of broadening the topic for more stakeholders and deepening it for important stakeholders.

Optimal Scope

The scope of a topic refers to its relative degree of inclusiveness as reflected in the elements of the PICOTS, key questions, and analytic framework. Defining the scope of a topic often requires striking a balance between (1) maximizing the comprehensiveness of a systematic and (2) accommodating the practicalities of conducting a timely review that produces precise and useable findings. Tradeoffs between breadth of scope and granularity may also be necessary for the systematic review findings to be clearly communicated. In the end, the scope of the topic should allow for a systematic review that is both coherent and sufficiently relevant and precise to be useful to decisionmakers.

The topic refinement team may consider many dimensions in determining the optimal scope; two of these are the intended conceptual scope and complexity. The intended conceptual scope of a review proceeds from the topic nomination. Although the topic is relevant to stakeholders, it may encompass separate and distinct sections. The topic refinement team must consider whether one systematic review should include all of the sections of the nominated topic. Does a high degree of inclusiveness allow for clear and precise key questions? Will a lower degree of inclusiveness include sufficient breadth to help stakeholders with decisionmaking? Systematic

reviews aim to gather and synthesize information from many disparate sources to help decisionmakers best weigh the benefits and harms of an intervention. A scope that is conceptually too narrow may not allow for effective decisionmaking. For example, one review might examine screening (a population health question), while a second review might examine treatment and/or management (an individual health question). Alternatively, a single review may effectively address the question of interest by focusing at a lower level of resolution.

Another dimension of scope is complexity. This pertains to the granularity of the key questions and PICOTS, and reflects Key Informant input and the characteristics of the literature. The topic refinement team must consider how inclusive they will be of the complexity of decisionmaking and the characteristics of the literature in shaping a scope that is both useful and applicable. Key Informant input may point to a variety of interventions and contextual factors. The evidence base may have a diversity of study types, different measures for a particular outcome, or variability in the delivery of interventions (e.g., as related to the mode of delivery, implementation characteristics, duration, and intensity). In light of this, both Key Informant input and the particulars of the evidence base may influence the development and specificity of the key questions and PICOTS. The topic refinement team must craft concise key questions that are both pertinent to stakeholders and methodologically relevant to the literature base. Questions that lack sufficient clarity may be cumbersome or too complex to answer, while those with higher granularity may not allow sufficient synthesis to provide useable conclusions.

To illustrate the concept of scope complexity, we offer the example of a literature scan for therapies for the management of Autism spectrum disorder (ASD) in children.⁷ The initial scan identified more than 3,600 articles, an estimated 20 percent of which were relevant to ASD therapies. The literature reported a variety and diversity of behavioral, medical, and complementary interventions comprised of small studies (mainly case series, case reports, or short-term trials). In addition, targets of interventions varied and included core symptoms of ASD, associated symptoms, and long-term functional outcomes.

Regardless of the volume of literature, the characteristics of the evidence base presented challenges in analysis and synthesis. The original nomination⁸ asked about effective interventions for treatment of ASD, and whether effects differed by diagnosis type, age, or severity. The topic refinement team then crafted key question and PICOTS to reflect the diversity and complexity of interventions, and the types of outcomes reported in the available literature. Resultant questions included, “What are the effects [of available behavioral, educational, family, medical, allied health, or CAM treatment approaches] on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors), in the short term (less than 6 months)?” This question reflects how the topic refinement team categorized interventions broadly by approach to capture the most information. The diversity of intervention components and programs and study types precluded the topic refinement team from developing key questions and PICOTS that could specify a more granular synthesis of the available literature. Nonetheless, the key questions and PICOTS yielded a systematic review that produced useable and applicable findings for stakeholders.

Researchability

A researchable topic has questions that are clinically and scientifically relevant, clear, precise, and answerable by a systematic review. The initial topic nomination may capture the importance, relevance, and decisional uncertainties faced by stakeholders. However, it will usually require refinement to arrive at questions that are suitable for a systematic review.

Considerations of researchability include the complexity of questions to be answered, clarity and precision of the key questions and PICOTS, consistency with clinical logic, and heterogeneity of the PICOTS elements. Other factors include the volume of literature and its impact on the timeliness and feasibility of the proposed review. Systematic reviews aim to help people make informed decisions about healthcare. Thus, a question may lose relevance if not answered in a timely way with the most up-to-date information. Relevance may also decrease if a question fails to account for the complexity and diversity of factors involved in the decisionmaking of a stakeholder.

This point is illustrated by a topic nomination that posed the question, “Can screening and surveillance for colorectal cancer using fecal DNA analysis improve health outcomes?”⁹ To answer this question, the topic refinement team considered test characteristics, its potential use in clinical practice, patient-centered outcomes and considerations, current practices and guidelines for colorectal cancer screening, and the current state of the evidence. The team then developed relevant questions consistent with EPC program Methods Guidance¹⁰ about absolute test characteristics alone and in combination with other tests, relative test performance compared to established screening modalities in practice, analytic validity, acceptability and adherence to testing, optimal screening intervals, impact on patient-centered outcomes, and harms. An analytic framework displayed the clinical logic behind the key questions and the relationship of the questions to each other. Input from Key Informants and the public further clarified the questions. Ultimately, all of these questions together were asked in order to fully answer the nominator’s original question.

Responsiveness to Stakeholder Input

Topic refinements should be responsive to diverse stakeholder input in order to reduce the potential bias of singular views, avoid investigator tunnel vision, and ensure balanced stakeholder input for the use of public resources. An open process with multiple stakeholders, including those making public comments, respects the plurality of voices and provides a forum in which to raise concerns or questions about what is important.

Topic refinement is a deliberative process, but not a consensus making activity; stakeholder consensus is not required. The process includes Key Informants who differ in their vested interests, values and priorities, and points of view as to the relevance of various factors in making health care decisions. Consensus may arise spontaneously, providing the EPC some level of confidence that the key questions are on target. However, lack of consensus may offer equal value by highlighting an area of conflict for the team to pursue in order to provide evidence to resolve such conflict.

EPCs should be carefully responsive to public comments received during the key question posting period. The value of public comments should be respected even if they are not as well informed as those of the Key Informant panel (i.e., it is important not to be dismissive and inadvertently miss out on an important insight). However, the team should reasonably weigh the public and Key Informant input accordingly.

Reducing Investigator Bias

The EPC program’s systematic review process aims to produce reports that are transparent, unbiased, credible, and comprehensive. Investigators obtain and weigh various inputs, then mold the topic scope with balance and impartiality. Investigators should be conflict-free regarding the topic being refined. Investigators systematically and consistently obtain input from diverse

stakeholders (via Key Informants and the public) who may challenge the assumptions of both investigators and researchers, identify gaps or inconsistencies in thinking, and provide context related to values and priorities. The topic refinement team is open to and respectful of input, and mindful of declared conflicts of interest of Key Informants. The team carefully considers all input, and transparently documents decisions and rationales. The relevance and credibility of the final product rests upon a systematic, transparent and consistent process, knowledge of and attention to potential conflicts of interest, and openness to diverse input all contribute to the relevance and credibility of the final product.

Transparency

Documentation of the topic refinement process should be adequately transparent. Evidence and considerations that influenced crucial topic refinement decisions and the rationale underlying critical refinements should be clearly and explicitly described, along with any constraints specific to the EPC program. This principle is important for public accountability, scientific rigor, and efficiency in the subsequent steps of conducting the systematic review.

Whitlock et al.⁵ have 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, with particular interests or investments in specific populations, interventions, or outcomes. Interested parties should be able to determine if and how their priorities were considered in the topic refinement process. Not all stakeholder interests will necessarily have been included in the topic refinement process, but transparency allows for public accountability.

Reproducibility is essential to scientific research. To be reproducible, the experimental methods must be thoroughly and transparently documented. Transparency in reporting can also provide important insight into how the research process affected the outcome. While the inherent and unavoidable subjectivity in the topic refinement process preclude its replication as in a controlled experiment, 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. Transparent documentation of the process allows a critical reviewer or a stakeholder to understand the basis upon which particular refinements to the topic were made. Descriptions of the influence of specific assumptions, evidence, stakeholder input, and rationales ensure a transparent report that provides context for understanding and assessing the strengths and limitations of the topic.

Transparent documentation of the topic refinement process can also add value to subsequent stages of the systematic review. In the course of conducting a systematic review, emergent questions may carry implications for the review's scope, PICOTS, and/or key questions. Questions may come from members of the systematic review team or from the elicited input of technical experts. Questions may also arise from evidence that surfaces during the systematic literature review. Such questions may or may not have been previously considered during topic refinement. A transparent record of the topic's evolution, with clearly stated descriptions of the factors and thinking behind refinements, is essential. Such transparency improves the efficiency

and coherence of the systematic review process by avoiding unnecessary duplication of effort on previously addressed questions and by providing background context in light of which new questions can be considered.

The EHC Program's approach includes the use of the previously described Topic Refinement Template for summary reports of individual topic refinements. However, summary reports from different EPCs displayed considerable variability in the detail and transparency of documentation about the factors and rationales that influenced important refinement decisions. The Topic Refinement Template provides a format that may be used for thorough and transparent documentation, but it does not include explicit instructions or a structure to assure that this standard of reporting is met. Therefore, in developing recommendations for the effective practice of topic refinement, our work group also identified some important updates for improving the guidance related to transparency in the Topic Refinement Template. Our recommended updates to the template are currently in process, and we detail them here.

Documentation of topic refinements will be more reliably transparent with more explicit instructions and a structured guide for more complete reporting of the evolution of the topic in the Topic Refinement Template. Instructions would include examples to convey that the report should not be comprehensive in detail, but should provide adequate and concise descriptions of the most important and/or potentially controversial topic refinement decisions. A tabular appendix to the report would show the evolution of the PICOTS, key questions, and analytic framework as the topic moved through the sequential phases of refinement: original nomination, initial refinement, Key Informant input, synthesis of input prior to public posting, and the refined topic. For each of these phases, the table would indicate specific changes made (if any), and the basis for the change (i.e., evidence, considerations, principles, and rationale). Such tables could serve as maps of the process and refinements for each topic.

The refined topic is posted for one month of public commentary after incorporation of Key Informant input and before completion of refinement. Of note, the current public posting document contains the PICOTS, key questions, and analytic framework, but does not include the complete topic refinement summary report. The EHC Program could consider whether the principle of transparency relevant to public accountability would be enhanced through posting of the complete topic refinement document.

Transparency differs from the guiding principles previously discussed. Transparency mainly governs the *process* of topic refinement rather than actual refinement decisions. The final product of topic refinement (i.e., the PICOTS, key questions, and analytic framework) can be assessed in regard to the principles of fidelity to the original nomination, relevance, scope, and researchability. The concept of transparency, however, applies not so much to the final product as to the description of the *production* of the final product. In this regard, transparency is similar to the principle of responsiveness (described above).

Other Programmatic Considerations

As noted above, topic nominations are initially assessed to determine whether they fulfill the EHC Program topic selection criteria used to determine the appropriateness of topics for systematic review. These criteria are appropriateness to the EHC program, importance, duplication, feasibility, and potential value.⁵ This commonly takes place in a limited amount of time and with a limited literature scan.

Infrequently, the topic refinement team may discover after topic refinement has begun (perhaps through input from Key Informants or a more detailed literature scan) that that the topic

as proposed no longer fulfills these selection criteria. In those instances, if the topic cannot be framed differently to yield a scope that will fulfill the selection criteria and the guiding principles described here, the topic may not proceed to a systematic review. Even though the considerations and purpose of topic development and topic refinement are separate and distinct, a topic in the refinement period must still fulfill the original selection criteria.

For example, during the topic refinement process for point-of-care testing for hemoglobin A1c (HbA1c), the topic refinement team learned that a systematic review on the same topic was underway.¹¹ 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 disease¹² 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 views of the Key Informants). Considering these factors, the team proceeded with a different type of EPC report rather than a systematic review. The alternative report was ultimately 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, including: the initial refinement phase, in which the provisional PICOTS, key questions, and analytic framework are developed; integration and synthesis of information and input from various sources, including Key Informants; reporting of the refinement process and resulting refined topic; and posting of the key questions for public comment. The primary goal of topic refinement is to formulate research questions that can be answered by a systematic review; the goal of topic refinement is not to answer the key questions.

As we described in our Introduction, the “Topic Refinement Template” (Appendix A) serves as both a guide to the various phases of the topic refinement process and as a template for the associated summary reports. The document also provides a record of the specific refinements made, along with the considerations and rationales that influenced the refinement decisions.

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., stakeholder engagement) may lead to a revision in the outcome of a previous phase (e.g., initial key question). 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.

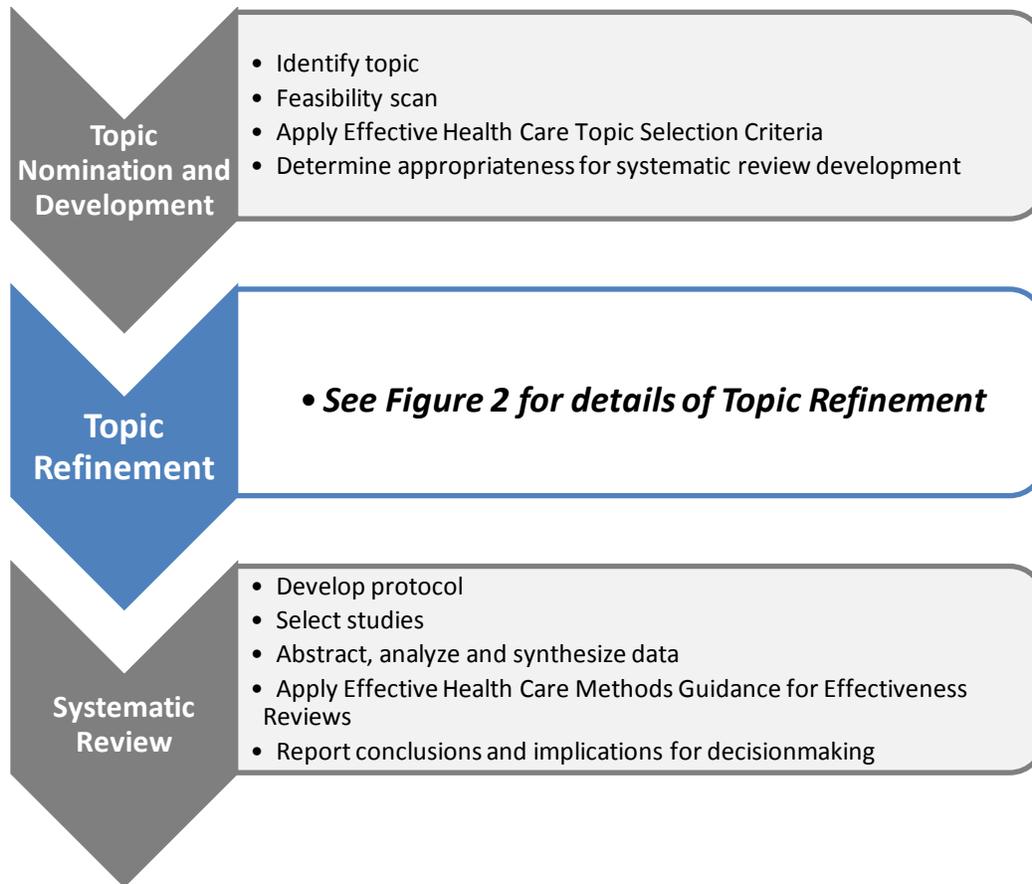
The following sections are intended to help topic refinement teams determine how to effectively conduct each phase of the process. The first section overviews topic refinement in the context of systematic reviews as conducted within the EHC Program. Each subsequent section addresses a different part of the overall process of bringing a topic from its original nominated form to its refined form for public posting, including potential considerations for each phase.

Given the variability between topics and topic refinement teams, these discussions are not meant to be prescriptive. Rather, they provide guidance for considering the advantages and disadvantages of various approaches to the phases of topic refinement.

The Relation of Topic Refinement to the Systematic Review

Topic refinement is one of many steps in the life cycle of a systematic review conducted through the EHC Program; it bridges the topic nomination and development and conduct of the systematic review. While we discuss topic refinement as a discrete step in the overall process, it is actually one part of a continuous, interconnected process that moves from topic nomination development and selection to the finished product. The lines can blur between one step of the systematic review process and the next. Figure 1 below outlines the steps in a systematic review that bracket topic refinement.

Figure 1. Topic refinement steps in a systematic review



The topic nomination and development team, whose work precedes topic refinement, determines if a nominated topic meets the EHC Program’s criteria to conduct a systematic review. Some topics exit topic nomination and development with fully developed key questions. However, the overwhelming majority of topics arrive at topic refinement with little more than a feasibility search, broad scoping boundaries, and a draft set of PICOTS. The topic nomination and development team ensures that the overall topic is “researchable” and relevant, without delving into the specifics of key questions or analytic framework.

After receiving a topic from the topic nomination and development team, the topic refinement team refines the topic into a scientifically valid question that can be researched using systematic review methodology, while adhering to the guiding principles outlined earlier. In addition to their own expertise and research experience, the topic refinement team may call on the assistance of content experts and important stakeholders. Further details on the topic refinement process are described in the sections below and outlined in Figure 2.

As noted earlier, substantial overlap may occur between each stage of the systematic review process. Although the formal work of topic refinement may be complete when the topic is given to the systematic review team, further evolution of the scope, key questions, analytic framework, and PICOTS may be needed. Thus, members of the topic refinement team may remain engaged in the topic beyond the formal end of that research phase. Additionally, the systematic review team may wish to initiate involvement in the project before commencement of the formal review phase. Thus, the systematic review team and the topic refinement team may collaborate in responding to issues or questions raised during the public commenting period.

Regardless of when topic refinement starts and ends, the goal is the same: to conclude the topic refinement process with a clearly defined set of key questions, analytic framework, refined PICOTS, and a defined scope narrow enough to be researchable, but broad enough to be useful to a wide array of stakeholders and end users. EPCs work towards this same goal, aiming to produce final topic refinement briefs that incorporate input from a broad array of Key Informants. EPCs may, however, use different strategies to reach that end. Here we detail various strategies with their respective strengths and weaknesses.

AHRQ's topic nomination and development team and the SRC have shared predominate responsibility for the work leading up to topic refinement, which results in a fairly uniform process. In contrast, each EPC has developed its own method for handing off topics from the topic refinement phase to the systematic review phase. In some cases, different investigators are responsible for each phase, a practice that may help ensure that the topic maintains maximum fidelity to the original nomination. For example, a systematic review team may wish to narrow or change the scope of a review in order to reduce the volume of literature and heterogeneity found across primary sources. However, scoping a topic too narrowly may reduce the report's usefulness to a wide range of stakeholders and end users. Designating a team of independent investigators to be responsible for just the topic refinement phase has other advantages, as well. For example, this strategy can allow for topic refinement to be conducted by individuals who are highly skilled at stakeholder engagement and experienced in developing focused and researchable key questions and analytic framework.

However, when the topic refinement and systematic review phases of a review are independently conducted, the topic refinement team may lack the content area knowledge required to sufficiently and appropriately scope a topic without input from additional content experts. In this case, topic refinement teams may wish to engage a local content expert to assist in the refinement process.

In contrast, other EPCs have developed a model where the same team of investigators conducts the topic refinement and eventual systematic review. In these cases, although the same team conducts both phases, leadership may shift from one phase to the next. For example, the lead investigator for the topic refinement phase may be highly experienced in stakeholder engagement, while the lead investigator for the systematic review phase may have content expertise or more experience in systematic review methodology. This approach further blurs the boundaries between the end of the topic refinement phase and the beginning of the scientific

research phase of a review. Ultimately, both staffing approaches to topic refinement have advantages and disadvantages, and EPCs may adopt a hybrid approach to staffing the topic refinement process.

Figure 2. The process of topic refinement



Note: AHRQ=Agency for Healthcare Research and Quality, EHC=Effective Health Care, EPC=Evidence-based Practice Center, PICOTS=population, intervention, comparator, outcomes, timing, and setting.

Initial Topic Refinement Phase

Background

The overall objective of the Initial Topic Refinement Phase is to develop “provisional” PICOTS, key questions, and an analytic framework. All of these will be used for Key Informant interviews and the subsequent phases of refinement, through which they may be refined. We discuss these elements of the initial topic refinement below. In addition, the topic refinement team should identify issues for discussion with stakeholders in the Key Informant interviews that take place after the initial topic refinement. These discussion issues may be related to technical questions, controversies with the topic, and/or stakeholder values and priorities.

Typically, the topic refinement team receives a topic triage package produced during the topic nomination, selection, and development phase. These documents represent the starting point of the topic refinement phase. The triage package includes the original nomination and a summary of the EHC Program selection criteria, existing guidance, and relevant literature. This information serves to inform the EPC about the nominator’s key decisional dilemmas; the previous topic triage discussions between AHRQ and SRC leading to topic selection; proposed topic modifications, if any; and recommended experts to serve as Key Informants or technical experts in the systematic review. The topic triage coversheet may also include preliminary PICOTS brought up during earlier discussions.

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 provide background information to help the topic refinement investigators better understand the topic and decisional dilemmas; and (2) to familiarize the team with the extent of the relevant literature. The literature scan should be a targeted yet systematic search and review of the scientific evidence. Rather than being fully synthesized, this supplemental literature scan simply informs the researchability, relevance, and scope of a subsequent systematic review.

The core members of the topic refinement team need not be experts in the topic at hand. Often, core members will conduct informational interviews with local topical experts. These interviews, which occur during the initial refinement phase, provide the team with needed insight about technical issues, controversies, and the current state of knowledge about the topic. Specific interview questions should be crafted to help the topic refinement investigator clarify basic issues of the topic or uncertainties that arise in the course of reviewing the topic nomination materials and the literature scan.

Based on a thoughtful and critical review of the literature scan, input from local experts, and discussions among themselves, the team develops the provisional PICOTS, key questions, and analytic framework. 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, key questions, and analytic framework are interdependent and complementary, and usually evolve together—with changes in one usually carrying through to the others. This process is rarely linear; certain aspects of the topic will fall into place before others, in no set order. Furthermore, a change in one aspect of the PICOTS or key questions may require changes in other aspects, and so on, until the pieces fall together.

Appendix B provides an example from an actual review to illustrate the refinement of a few specific aspects of a topic. The diagram 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. The table below the diagram charts the identified need for changes to select 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—an approach that can be comprehensively applied to the initial refinement of all aspects of a given topic.

PICOTS

To clearly articulate a topic, one must clearly articulate the basic components of interest. These include: population(s), intervention(s), comparators, outcome(s), timing, and settings — collectively referred to as the PICOTS.^{5, 13} These basic components underlie the key questions that guide the systematic review. The PICOTS reflect the scope of the review and determine its inclusion criteria. Preliminary identification of the PICOTS of interest might occur during the phases of topic nomination and triage; however, the PICOTS are more fully developed during the initial topic refinement. Refining the PICOTS of interest will often involve balancing several considerations, because the inclusion of one element might have restrictive implications for other elements. For example, a particular outcome may be of principal or exclusive interest, and certain interventions may be incompatible with that outcome. Similarly, constraining the populations of interest may restrict relevance to only certain interventions or outcomes. When making balanced decisions about the PICOTS of interest, the topic refinement team should consider the principles discussed above, including fidelity to the nomination, scope, relevance, and researchability.

Another overarching principle that should guide the formulation of provisional PICOTS is their patient-centeredness and relevance for decisionmaking.⁵ For example, the choice of the comparators of interest should be guided by consideration of comparative effectiveness of the intervention of interest against comparators that represent current standard of care as opposed to placebo or no treatment. Outcomes that are longer-term or that measure quality of life are more important than short-term outcomes of drug pharmacodynamics and pharmacokinetics, which should be of secondary interest. PICOTS should also be formulated independently of what the topic refinement team or stakeholders anticipate may or may not be found in the primary literature. Whitlock et al. describe in detail the principles that best guide identification and development of the PICOTS.⁵

Key Questions

The key questions guide the systematic review. These questions serve as the basis for the review protocol, including the criteria for inclusion or exclusion of studies. Well-written key questions should be precise, detailed, and clearly focused. The questions should 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.

The configuration and ordering of the PICOTS elements in the key questions will vary according to the details of the topic and the discretion of the investigators. However, the goal should always be to formulate clear questions that elucidate the important health care issue of interest. Good key questions are formulated without judgments about the likelihood of the extant literature to answer them. See Appendix B for an example of well-written provisional key questions.

Broadly speaking, the key questions address patient-centered health outcomes, which are also referred to as ultimate health outcomes of interest (e.g. quality of life, mortality, clinical events, hospitalization, etc.), intermediate outcomes (e.g. diagnostic performance of a test, surrogate makers, etc), outcomes of harms, and factors that may variably influence effect estimates. To more precisely describe factors that may be variably associated with outcomes, subsidiary key questions may be used. Subsidiary key questions expand on the basic key questions to further specify subpopulations, different forms of the intervention, or specific settings that might affect the outcomes of interest.

The Analytic Framework

The analytic framework is a graphic representation of the relationships between the elements of the PICOTS of interest and the key questions. Along with the key questions, the analytic framework informs the scope of the review and the study eligibility criteria. The analytic framework depicts the causal pathways for the effects of an intervention. In other words, it diagrams our understanding of the clinical, biological, or health services underpinnings of the mechanisms through which an intervention is presumed to effect changes in outcomes. As noted, outcomes of primary interest are those that are patient-centered and ultimately of most importance to patients, consumers, and decisionmakers. Such patient-centered outcomes occupy the final causal position in the framework. Outcomes thought to be causal intermediates or surrogates of the primary outcomes are depicted as proximal and indirect points in the causal pathway. These “intermediate outcomes” are only important if they are shown to be associated with patient-centered health outcomes.

Particular key questions are generally associated with particular arrows in the framework. Logical relationships between the key questions and the PICOTS and of the key questions to one another are clearly depicted. 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 most important question investigates effects of the intervention on the patient-centered outcomes of interest; this graphic representation is very clear in most analytic frameworks. If the evidence for this question is suspected or found to be insufficient, a series of additional questions may investigate the intervention’s effect on intermediate outcomes and their association with patient-centered outcomes. Again, the relationship of these intermediate questions to the question of ultimate patient-centered outcomes can be made clear in the framework. The framework has been described in more detail previously.^{10, 14-16} An example of a simple analytic framework is in Appendix B.

Engaging Stakeholders as Key Informants

Systematic reviews conducted by EPCs through the EHC Program are designed to address health care questions of relevance to patients, clinicians, agencies that issue guidelines, policymakers, industry, and/or health care organizations. These reviews are most useful when the questions they address accurately reflect the needs, values, and priorities of those who will actually use them. To that end, the EHC Program includes stakeholders in the process of topic refinement. Stakeholders are those persons or groups affected by the clinical or policy decisions that a systematic review is designed to address. The topic refinement team conducts interviews with Key Informants, who represent particular stakeholder categories. The team elicits Key

Informants' views on the topic to gain insight on specific decision points that arose during the initial refinement.

Purpose

What we learn through research depends on the questions that we ask. Traditionally, researchers and funders of research have been the sole decisionmakers in determining which questions are significant. To improve the applicability and relevance of systematic reviews for health care decisionmakers and those affected by their decisions, the EHC Program is committed to enhancing and expanding public involvement in its research endeavors.⁶ One way to achieve this goal is to formally and broadly engage stakeholders in the process of refining the questions to be addressed by systematic reviews.

Key Informant interviews serve to elicit informants' opinions about the accuracy, relevance, and importance of the preliminary key questions and analytic framework developed in the initial refinement. Key Informants also provide input about issues not adequately addressed with the limited literature scan or discussions with local experts. Key Informant interviews provide a spectrum of relevant views to inform the topic refinement team about technical aspects of the topic, stakeholder priorities, and potential dilemmas or controversial decision points.

The Key Informant interviews provide an open process through which various viewpoints and expertise are recognized and respected. Consensus is not necessarily the goal. Rather, the topic refinement team makes decisions through the deliberative process of collecting, synthesizing, and integrating stakeholder input. The team may not ultimately incorporate all Key Informant input into the topic. As noted previously, topic refinement decisions are influenced by multiple factors, of which stakeholder input is just one. Whether or not informants' input is ultimately incorporated into the topic, the topic refinement summary report should include a transparent discussion of the salient issues that arise in the interviews and the rationale for the team's decisions regarding those issues.

The configuration and facilitation of the Key Informant group will likely affect the type of input that the topic refinement team receives from stakeholders. The topic refinement team should carefully consider inclusion of relevant stakeholders, thoughtfully determine the composition of the specific Key Informant interview groups, and skillfully conduct the actual interviews.

Identifying and Recruiting Key Informants

Key Informants for a topic should represent the most relevant stakeholders and the particular types of expertise deemed most useful by the topic refinement team. The topic refinement process must be completed within a limited timeframe that fits within the other steps of the systematic review. Therefore, the refinement team cannot possibly engage all conceivable stakeholders. Instead, investigators must decide which stakeholder groups are critical for the topic and then identify the Key Informants to represent those groups.

Because the team will have developed some understanding of the topic—its general relevance, its relevance for particular stakeholder groups, and related controversies or dilemmas—they should have a reasonable idea of potential stakeholders to include. The team can begin by generating a list of stakeholder categories from which to search for Key Informant representatives. The individual Key Informants might be identified by contacting professional, industry, or advocacy organizations; by contacting experts whose publications are reviewed in the literature scan; by referral of the AHRQ Task Order Officer, who may know of relevant

stakeholders who have participated in the EHC Program; by referral of local experts; or by referral of potential Key Informants (both those who elect to participate and those who do not). When identifying potential informants, the team may also inquire about other critical stakeholders not yet identified who should be included. The topic refinement team may also receive a list of suggested stakeholders from the topic nomination, selection, and development phase.

Recruitment and scheduling of Key Informants can be time consuming. Generally it requires multiple communications, coordination of schedules, and completion of required paperwork such as that related to possible conflicts of interest. Some potential informants will decline to participate or will be unavailable during the designated timeframe. Therefore, making a prioritized list of more than one potential informant for each stakeholder category is helpful. The initial invitation to participate should include a brief introduction to the EHC Program, a description of the topic and the interview process, and information about the time and preparation required to participate. 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 informants. Based on a number of factors, the Key Informants might be interviewed in groups of various sizes and composition, as described in more detail in the next section. The topic refinement team should define the optimal size and composition of the individual interview groups, and try to schedule the required interviews accordingly.

The topic refinement team should ensure that the Key Informant group represents the diversity of viewpoints on and interests in the topic. Unless clearly not relevant for a particular topic, patients or their representatives should 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, informants representing the important opposing viewpoints should be enlisted.

Composition of Key Informant Interview Groups

When deciding how to group Key Informants for the interviews, the topic refinement team should consider several factors, including the number of informants in a group, the particular stakeholders included, and the relative heterogeneity of the group. Decisions about these factors may involve tradeoffs. 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 a technical issue requiring certain expertise, the size and heterogeneity of the group would likely 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). 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 participating in a single interview may affect the likelihood that all participants will fully express their opinions, 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 exploring 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 very 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 does not often outweigh the disadvantages. Therefore, the topic refinement team should generally avoid convening interview groups that are too large.

An optimal number of Key Informants for a single interview would avoid the above problems of an overly large group while providing a sufficient variety of relevant viewpoints to assure good interactions and a fruitful discussion. Different interview groups may be convened to focus on different specialized aspects of a single topic, or all groups might focus on the same aspects of the topic. In either case, the topic refinement team should carefully select the participants for each group to assure a complementary mix of expertise and viewpoints well matched to the issues to be discussed. The group may represent a more or less heterogeneous mix of stakeholders depending on the particular questions or controversies to be explored.

Determining the optimal 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. The specific issues and questions related to the particular topic will also affect decisions about the size and composition of interview groups. However, for most topics, two to four Key Informants are optimal. For eliciting very specialized and/or voluminous information, one-on-one interviews with particular informants may be beneficial. The disadvantages of one-on-one interviews include the extra investigator time required and lack of interaction between stakeholders of different perspectives. One-on-one interviews can also be used as a back-up means of engaging informants whose schedules do not coincide with those of the other informants.

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. Generally, the team conducts interviews over a period of no more than 3 to 4 weeks, with several additional weeks in which to synthesize and incorporate the informants' input. Thus, these interviews are not conducted with the same high level of methodological and analytical rigor that would be used in the best focus group research (e.g., coding of transcripts, reaching saturation). Rather, these interviews are an efficient way of eliciting input from a critical set of 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 should be scheduled to allow adequate time (ideally about 60 to 90 minutes). Typically a core member of the topic refinement team facilitates the interviews, and at least one other member of the team attends and takes notes. Recording and transcribing the interviews can provide a more complete record for referencing later when documenting the interviews for the summary report.

Adequate preparation is essential to successful Key Informant interviews. To this end, Key Informants should be sent advance materials that reiterate the general purpose of topic refinement (i.e., to formulate research questions, not to answer them) and clarify their role in the process. They should also be sent a document that includes the provisional PICOTS, key questions, and analytic framework developed during the initial refinement. Finally, the informants should be sent a list of the salient issues and questions for use in structuring and

guiding the discussion. This list should be developed in the course of the initial refinement and should represent the main decision points and/or points of factual information on which the topic refinement team requires stakeholder input. These questions should be well considered, not generic. The list should also include an open-ended question that invites Key Informant input on any aspect of the topic, PICOTS, key questions, or analytic framework that was not explicitly mentioned. The wording of the guiding questions should be compatible with the backgrounds of all of the interview participants, which may require some tailoring for individual groups. Guiding questions should avoid the use of technical jargon that might be unfamiliar to some informants.

Experience suggests that not all Key Informants will read the preparatory materials before the interview and that some will not understand every element. For this reason, but also to reiterate and clarify the meeting's purpose before the interview begins, the facilitator may open 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.⁶ 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, whether 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 informants. The facilitator should also avoid technical jargon when possible, and should define it when it cannot be avoided. 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 especially 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. Questions targeting a specific informant in a mixed group can be useful and necessary, but these should be the exception, not the rule.

Frequently, a Key Informant will make a point or express an opinion that raises more questions than it answers. In those cases, the topic refinement team may find it valuable to explicitly incorporate the new question into subsequent interviews in order to elicit further input on the issue from other informants.

Synthesizing and Incorporating Key Informant Input

Ultimately, the topic refinement team decides how to incorporate Key Informant input. A detailed record of the interviews can be useful for reliably considering all relevant Key Informant 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. At least one member of the team should take notes during each interview. Recording and transcribing the interviews provides an even more complete record. Team members from at least one EPC use a standard form at each interview to record the most salient points raised by informants regarding each element of the PICOTS and to note whether or not the discussion implied the need to make any specific changes to the PICOTS, key questions, or analytic framework. This form provides a structure for team

debriefing after the interview. The form also helps ensure that important issues are not missed in the synthesis once the all interviews have been completed.

Finally, the topic refinement summary report should include a clear narrative of the characteristics of engaged stakeholders, the most important and/or critical issues raised, and the disposition of those issues. The narrative should transparently describe the discussion of these issues within and across the various interview groups, clearly delineating important points of agreement or disagreement among informants. The narrative should clearly reveal the rationales behind the team's decisions regarding each issue.

Integration and Synthesis

The initial topic refinement phase and Key Informant interviews require consideration of many issues related to the PICOTS, key questions, and analytic framework. Some aspects of the topic will fall into place before others, at different phases of the process, and in no set order. During the initial topic refinement phase, a local expert might provide necessary and sufficient input to definitively settle a technical issue that arose during the team's original scan of the literature. Similarly, the input of one or more Key Informants might suffice to definitely inform the topic refinement team's decision on an aspect of the topic, such as the included population or a particular outcome of interest. Frequently, however, questions will remain unsettled through much or all of the topic refinement process—perhaps because the question at issue is particularly complex, contentious, or controversial and not easily settled. Or, the topic refinement team may intentionally delay deciding on a question until they have gathered input from Key Informants representing the breadth of stakeholder perspectives. Occasionally, due to the interrelatedness of the various aspects of a topic, an issue previously settled must be reconsidered in light of a subsequent decision regarding another aspect of the topic.

For questions that remain unsettled after the initial topic refinement phase and Key Informant interviews, the team should carefully and systematically consider all relevant technical issues, stakeholder perspectives, and guiding principles. To reach a decision, the team may discuss these issues among themselves and with the task order officer. The Topic Refinement Template is useful for structuring the synthesis of the literature scan, the Key Informant input, and the topic refinement team's thinking on decision points. As with other aspects of topic refinement, balancing these considerations against one another requires the thoughtful judgment and discretion of the investigators.

Reporting

Changes in a topic may occur at discrete points in the topic refinement process. The initial topic (as defined in the topic nomination and development phase that precedes topic refinement) may change as the topic refinement team, informed by the literature scan and local experts, prepares their provisional PICOTS, key questions, and analytic framework. Further changes often occur in response to Key Informant interviews and, if undertaken, a revised literature scan. When necessary, the last set of changes can occur in response to public comments. Changes to the topic depend on the types of stakeholders engaged and the quality of their input, the manner of balancing of these inputs, and considerations of feasibility. The multiple opportunities for refining and modifying a topic underscore the importance of transparently and consistently reporting and summarizing the changes and rationales used in refinement 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.

Through the topic refinement summary report, the team (1) objectively documents the evolution of a topic and explains decisions, particularly when there is a clear alternative; (2) points to areas of conflicting input; and (3) highlights areas that remain unresolved. They may also use this report to trace their own rationales for changes through the topic refinement process. For the evidence review team, the topic refinement summary report provides an historical document to be used 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, and contribute to discussion of future research needs in the evidence report. The task order officer may refer to this document to respond accurately to stakeholder queries, and to ensure the consistency of scope changes with EHC principles and criteria. The full topic refinement summary report is not posted publicly. However, the analytic framework, PICOTS, and key questions are reported publicly during public posting period, in the protocol, and in the evidence report.

The reporting elements in the topic refinement summary report (see below) balance the principles of transparency and scientific integrity with the need to be concise. This poses a challenge because the very intent of topic refinement is to make changes in response to various inputs. The reporting elements of topic refinement are:

- A background section that includes the rationale for the proposed review, describes currently available interventions and practices, delineates proposed advantages and disadvantages of various interventions, highlights clinical or decisionmaking uncertainty that may affect patient care and outcomes, and outlines relevant contextual considerations.
- The initial key questions and PICOTS from topic development.
- Details of the preliminary literature scan.
- A brief summary of input from local experts.
- Provisional key questions, PICOTS, and analytic framework, developed with input from local experts.
- Issues for consideration by Key Informants.
- A brief summary of Key Informant interviews.
- The refined key questions, PICOTS, and analytic framework, developed with Key Informant input.
- Further refinements developed in response to input from public posting.
- The rationales for changes made in the course of the topic refinement process.

Topic refinement summary reports should include the standardized general elements outlined in the Topic Refinement Template (see Appendix A). However, the workgroup observed variability in the content and level of detail in individual summary reports, particularly in the following areas: (1) the documentation of local expert discussions; (2) the level of detail describing Key Informant input, though much greater detail was found in the Key Informant call minutes; (3) documentation of changes to key questions and PICOTS over the topic refinement process; (4) the explanatory language for changes made to elements of the key questions and PICOTS, especially those made prior to Key Informant input; (5) the level of detail describing issues or controversies, and how different priorities or inputs were considered or weighed by the topic refinement team; and (6) documentation of considerations given to the literature search. Additionally, the topic refinement summary report does not include formal documentation of (1) changes made after public posting of the draft key questions, PICOTS and analytic framework;

(2) and details of the initial literature scan. The workgroup noted that other documents generated in the course of topic refinement, such as call minutes with the task order officer and Key Informants, sometimes provided highly detailed documentation of discussions. However, the summaries found in the topic refinement summary reports may not have captured sufficient detail about the important issues and decisions that affected the topic scope.

To improve transparency and consistency of reporting, the workgroup recommended: (1) a more detailed description of important and/or potentially controversial issues that arose during the topic refinement process; (2) a summary of relevant points of the topic refinement team's discussion of issues that were considered controversial or that required balancing different inputs; (3) sufficient detail of rationales for changes, including what changed, the timing, and inputs considered (i.e., literature scan, Key Informant input, topic refinement principles); (4) inclusion of decisions that were considered, but did not result in a change at the time; (5) inclusion of decisions that will require additional future input (public commentary, Technical Expert Panel input, a more focused literature scan, etc.) or are more appropriate for the evidence review phase; and (6) documentation of these changes in a tabular format.

Public Posting

In addition to the value of input from diverse Key Informants, public posting offers an important means of capturing input from a broader arena of stakeholders. This also promotes transparency, another key aspect of the EHC Program. A document outlining the proposed scope is posted publicly on the EHC website for 4 weeks. This document includes the draft key questions, PICOTS, and analytic framework. It 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 particular stakeholders, relevance of questions, identification of 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, and affirm the need for a new review. For example, for a recent review on inguinal hernia repair,¹⁷ the Key Informants affirmed the importance and relevance of the topic and provided input about certain procedures not commonly performed in the United States. This input ensured that the review would focus on the most relevant procedures. It also 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. The group's collective input resulted in new key questions about watchful waiting as a management strategy for a symptom-free hernia, new key questions specific to pediatrics, and inclusion of additional patient-centered outcomes.

At the end of the posting period, the topic refinement and/or systematic review team reviews all comments and makes additional revisions if indicated. The team considers the perspectives of the commenters, considerations used in previous decisions, and earlier sources of input from the Key Informant panel, literature scan, local experts, and the original nominator while respecting

the guiding principles outlined earlier. The team also considers the potential impact of any changes in light of topic refinement principles. They document the specific responses to these comments in the topic refinement summary report. The revised key questions, PICOTS, analytic framework, and general highlights of comments and responses are then 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.

Box 2. Key points

- ❖ The goal of topic refinement is to define PICOTS, key questions and an analytic framework that result in a useful systematic review; it asks relevant questions, considers values of stakeholders in decisionmaking, reflects the state of the science, and is consistent with systematic review research methods.
- ❖ The guiding principles are: fidelity to the original nomination, relevance, suitable scope, researchability, responsiveness to stakeholders, reduced investigator bias, and transparency.
- ❖ The topic refinement team refines the preliminary topic with input from local experts, a literature scan, Key Informants, and public posting. They weigh the inputs carefully keeping in mind the guiding principles.
- ❖ The Key Informants include end-users of the systematic review and represent a diversity of viewpoints and perspectives. Processes for engagement should facilitate open input and active participation.
- ❖ All decisions should be concisely and transparently documented, with the rationale for the decisions clearly expressed.

Conclusion

AHRQ's Effective Health Care Program conducts systematic reviews on health care topics to address the needs of a broad range of stakeholders with interests in the design, organization and delivery of health care. What can be learned through these reviews depends on the questions asked. Traditionally, researchers and funders of research have been the sole decisionmakers with regard to which questions are significant. However, selecting the questions that research will answer presupposes judgments of value, which are not solely scientific judgments. To provide more broadly useful answers that reflect the perspectives and values of the users of the research, the EHC Program engages a variety of stakeholders. These stakeholders participate at numerous points during the design and conduct of systematic reviews, including in the original nomination of potential topics for review. The refinement of those stakeholder-nominated topics into a form that poses key questions of optimal relevance and researchability is critical to producing the most useful systematic reviews.

To date, EPCs in the EHC Program 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 and synthesized the approaches to topic refinement used by various EPCs. We critically assessed all aspects of the topic refinement process, and identified lessons learned related to both successful and unsuccessful strategies in topic refinement. We have developed a set of recommended guiding principles and identified effective approaches to consider when conducting a topic refinement.

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 practical principles for more systematic and explicit decisionmaking. Our recommendations should help investigators to determine effective approaches to conducting the refinement of individual topics. We hope that the use of these recommendations, both within and outside of the EHC Program, will make for a more thorough and rigorous process that produces topics refined to be optimally relevant and researchable.

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Abbreviations

Abbreviation	Definition
A1c/HbA1c	Hemoglobin A1c or Glycated Hemoglobin level
ASD	Autism spectrum disorder
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