

# APPENDIXES

# APPENDIX A

**XXX EPC Frameworks Project: Research Gaps Worksheet**

<Project Name>

**Research Gap Worksheet**

Completed by – \_\_\_\_\_

Date – \_\_\_\_\_

Page \_\_\_\_ of \_\_\_\_

Key Question Number – \_\_\_\_\_

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

\* Reasons for Gap -

- A. *Insufficient or imprecise information*
- B. *Biased information*
- C. *Inconsistency or unknown consistency*
- D. *Not the right information*

## Instructions for research gaps abstraction worksheet Dec 2010

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

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

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

### Reason(s) for Gaps

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

#### A. Insufficient or imprecise information

Insufficient information in identified studies can arise if no studies are identified, if a limited number of studies are identified, or if the sample sizes in the available studies are too small to allow conclusions. If the information available in identified studies is insufficient to allow a conclusion or if the estimate of the effect (usually achieved from a meta-analysis) is imprecise there is a research gap.

Correspondence to grading systems:

- *EPC SOE*: **Precision** is a required domain.
- *GRADE*: The GRADE Working Group advises decreasing the grade of the quality of the evidence if the data are “**imprecise** or sparse”.
- *USPSTF*: The following questions are considered while grading the evidence:
  - “How many studies have been conducted that address the key question(s)?”
  - “How large are the studies? (i.e., what is the precision of the evidence?)”

## B. Biased information

The aggregate risk of bias is contingent upon the risk of bias of the individual studies.[#19] In addition to considering methodological limitations of studies, the appropriateness of the study design should also be considered.

Correspondence to grading systems:

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

## C. Inconsistency or unknown consistency

Consistency is the degree to which reported effect sizes from included studies appear to go in the same direction. The two elements are whether effect sizes have the same sign (same side of ‘no effect’) and whether the range of effect sizes is narrow. However, it should be kept in mind that a statistically significant effect size in one study and an effect size whose confidence interval overlaps null in another study do not necessarily constitute inconsistent results. If there is only one available study, even if considered large sample size, the consistency of results is unknown.

Correspondence to grading systems:

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

## D. Not the right information

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

Correspondence to grading systems:

- *EPC SOE*: **Directness** is a required domain. It also incorporates the element of surrogate versus clinical outcomes.
- *GRADE*: **Directness** is a key element.
- *USPSTF*: The following question is considered while grading the evidence:
  - “To what extent are the results of the studies generalizable to the general US primary care population and situation? (i.e., what is the external validity?)”

## Characterization of Research Gaps

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

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

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

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

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

Setting (S) – In this column, when appropriate, team members should specify the relevant settings for research gaps.

## Special Considerations

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

Research gaps relating to the benefit of one form (or frequency) of clinical assessment (e.g., monitoring) versus another can be fit into the PICOS framework by considering these clinical assessments as intervention (I) and comparison (C). The comparison in this case could include a

standard form (or frequency) of clinical assessment or no clinical assessment. Relevant outcomes (O) could include clinical outcomes to assess the benefit of the clinical assessment(s).

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

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

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

# APPENDIX B

EPC Framework Evaluation Form

1. EPC Name

2. Date Form Completed - Month (mm) .....|\_|\_|

3. Date Form Completed - Day (dd) .....|\_|\_|

4. Date Form Completed - Year (yyyy) .....|\_|\_|\_|

5. During what stage was the evidence gap framework sheet completed?

**(Select only one)**

- Systematic Review
- Future Research Needs Document
- Other

6. EPC Project Name

7. Who completed the evidence gap framework sheet?

**(Select all that apply)**

- Principal Investigator
- Other Investigator
- Research Staff Member
- Other (list below)

8. Has your center previously identified gaps from systematic reviews?

- No (go to Q14)
- Yes (describe below)

**9. Previous Gap Identification - Describe**

10. Are there **advantages** to using this framework versus how you identified gaps previously?

- No (go to Q14)
- Yes (describe below)

11. **Advantages of Framework Sheet - Describe**

12. Are there **disadvantages** to using this framework versus how you identified gaps previously?

- No (go to Q14)
- Yes (describe below)

13. **Disadvantages of Framework Sheet - Describe**

14. Were there any problems or issues in using the evidence gap framework sheet?

- No (go to Q16)
- Yes (describe below)

**15. Problems Using Framework Sheet - Describe**

**16.** Do you have any suggestions to improve the efficiency and/or usefulness of the evidence gap framework sheet?

- No (go to Q18)
- Yes (describe below)

**17. Framework Sheet Suggestions - Describe**

**18.** Do you have any suggestions to improve the instructions for the framework sheet?

- No (go to Q18)
- Yes (describe below)

**19. Instructions Suggestions - Describe**

**20. General Comments**

**21. Contact Name** (of person completing this evaluation form)

**22. Contact E-mail**

**23. Contact Phone Number**

**Submit by June 7, 2012:**

XXXX

# APPENDIX C

XXX EPC Frameworks Project: Research Gaps Worksheet  
 Systematic Review ID: \_\_\_\_\_

Completed by – \_\_\_\_\_

Date – \_\_\_\_\_

Page \_\_\_\_ of \_\_\_\_

Key Question Number (Enter "99" if outside scope) – \_\_\_\_\_

Serial No.	Reason(s) for Gap*	Other Reason(s) for Gap	POPULATION (P)	INTERVENTION (I)	COMPARISON (C)	OUTCOMES (O)	SETTING (S)	Free Text Gap	Notes

**\* Reasons for Gap**

**Insufficient or Imprecise Information** → **A1**=No studies, **A2**=Limited number of studies, **A3**=Sample sizes too small, **A4**=Estimate of effect is imprecise

**Information at Risk of Bias** → **B1**=Inappropriate study design, **B2**=Major methodological limitations in studies

**Inconsistency or Unknown Consistency** → **C1**=Consistency unknown (only 1 study), **C2**=Inconsistent results across studies

**Not the right information** → **D1**=Results not applicable to population of interest, **D2**=Inadequate duration of interventions/comparisons, **D3**=Inadequate duration of follow-up,

**D4**=Optimal/most important outcomes not addressed, **D5**=Results not applicable to setting of interest

## **Instructions for research gaps abstraction worksheet**

Oct 2011

### Purpose

A research gap is a topic or area for which missing or inadequate information limits the ability of reviewers to reach a conclusion on a given question. This worksheet is designed to facilitate the identification, description and organization of research gaps during evidence reviews sponsored by AHRQ. When completed during the production of an EPC report, investigators would fill out this worksheet soon after the data synthesis phase, while in the process of writing the results section of the evidence report.

### Instructions

1. Enter name of EPC report or systematic review project in upper left hand corner.
2. Complete one or more worksheets for each review question (question included in the systematic review). Indicate question number in top right hand corner. (Enter “99” if gap is outside scope)
3. Initial and date each worksheet.
4. Number the worksheets.
5. Enter gaps into the table, per guidance provided below. In the worksheet table, each row is one research gap and is numbered accordingly (“Serial Number”).

### Guidance for completing table

#### **Reason(s) for Gaps**

Enter the reason(s) for the gap in the second column. The classification of the reasons for gaps are listed and coded in the legend of the gaps abstraction worksheet. Choose the most important reason(s) for the existence of the research gap. The reason selected should be the reason(s) that most precludes conclusions from being made about that question. Put another way, consider what would be needed to allow for conclusions to be made. If that particular reason(s) for gap was resolved, could the reviewer draw a conclusion about the question? Codes for more than one reason may be entered in this column, as appropriate. Reasons that cannot be fit within the defined coding system should be listed in the third column titled “Other Reason(s) for Gap”.

The reasons for gap are categorized as:

- A. Insufficient or imprecise information
- B. Information at risk of bias
- C. Inconsistency or unknown consistency
- D. Not the right information

For each of these categories, the relevant domain or element from the EPC Strength of Evidence, GRADE and USPSTF are listed. Work completed in grading the body of evidence should be used in completing this worksheet. It may be useful to review the most recent guidance about each of these evidence grading systems.

The specific reasons for gaps are listed in the footnote of the table and described below:

A. Insufficient or imprecise information

Information is insufficient or imprecise if data are sparse and thus uninformative and/or confidence intervals are wide and thus can include conflicting results or conclusions.

A1 – This reason should be selected if no studies are identified.

A2 – This reason should be selected if a limited number of studies are identified.

A3 – This reason should be selected if the sample sizes or event rates in the available studies are too small to allow conclusions.

A4 – This reason should be selected if the estimate of the effect (usually achieved from a meta-analysis) is imprecise. That is, if the width of the confidence interval is such that the conclusion could be for benefit or harm.

Correspondence to grading systems:

- *EPC SOE*: **Precision** is a required domain.
- *GRADE*: The GRADE Working Group advises decreasing the grade of the quality of the evidence if the data are “**imprecise** or sparse”.
- *USPSTF*: The following questions are considered while grading the evidence:
  - “How many studies have been conducted that address the key question(s)?”
  - “How large are the studies? (i.e., what is the precision of the evidence?)”

B. Information at risk of bias

The aggregate risk of bias is contingent upon the risk of bias of the individual studies.

B1 – This reason should be selected if the study design(s) are inappropriate to address the question of interest.

B2 – This reason should be selected if there are major methodological limitations to the available studies.

Correspondence to grading systems:

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

C. Inconsistency or unknown consistency

Consistency is the degree to which results from included studies appear to be similar or in concordance.

C1 – This reason should be selected if only one study is identified. If there is only one available study, even if considered a large sample size, the consistency of results is unknown.

C2 – This reason should be selected if the results from available studies are inconsistent. Elements to consider include whether effect sizes vary widely, if the range of effect sizes is wide, limited or no overlap of confidence intervals, and, as appropriate, if statistical tests, such as  $I^2$ , indicate heterogeneity.

Correspondence to grading systems:

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

D. Not the right information

There are a number of reasons why identified studies might not provide the right information.

- D1 – This reason should be selected if the results from studies might not be applicable to the population of interest.
- D2 – This reason should be selected if the duration of the interventions and/or comparisons is too short.
- D3 – This reason should be selected if participants are not followed up for long enough duration in the included studies.
- D4 – This reason should be selected if the optimal and/or most important outcomes are not assessed in the included studies. This reason also includes instances where only data on surrogate outcomes are available while data on more clinical and/or patient-important outcomes are needed.
- D5 – This reason should be if the results from studies might not be applicable to the setting of interest. This would include interventions not applicable or available in setting of interest.

Correspondence to grading systems:

- *EPC SOE*: **Directness** is a required domain. It also incorporates the element of surrogate versus clinical outcomes.
- *GRADE*: **Directness** is a key element.
- *USPSTF*: The following question is considered while grading the evidence:
  - “To what extent are the results of the studies generalizable to the general US primary care population and situation? (i.e., what is the external validity?)”

## **Characterization of Research Gaps**

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

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

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

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

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

Setting (S) – In this column, when appropriate, specify the relevant settings or aspect of setting not adequately addressed in evidence base.

### **Special Considerations**

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

Research gaps relating to the benefit of one form (or frequency) of clinical assessment (e.g., monitoring) versus another can be fit into the PICOS framework by considering these clinical assessments as intervention (I) and comparison (C). The comparison in this case could include a

standard form (or frequency) of clinical assessment or no clinical assessment. Relevant outcomes (O) could include clinical outcomes to assess the benefit of the clinical assessment(s).

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

Research gaps which are difficult to characterize into the PICOS framework should be abstracted in free text form. Interventions could potentially include a range of treatment options, order of treatment options, individualization of treatments, etc. These are often gaps for which it is difficult to identify a clear intervention or comparison of interest. It may not be possible to translate these gaps into appropriate research questions. Examples of questions derived from such research gaps are: “What are the optimal glucose thresholds for medication use in women with gestational diabetes?”; “In what order should patients with cystic fibrosis perform their airway clearance therapies?” and “How should physicians choose an airway clearance therapy for a given patient with cystic fibrosis?”

# APPENDIX D

**Evaluation of the use of the Research Gaps Framework  
by Evidence-based Practice Centers (EPCs)**

Seven EPCs evaluated the Research Gap Framework and submitted 8 evaluation forms (one EPC submitted completed evaluation forms from two different project teams).

We first provide a summary of the quantitative questions in a table. For each question asking for further details, such as a description of disadvantages, we include the text submitted with the EPCs and projects de-identified. For these questions we have added a column (XXX Response) that includes notes about changes to framework or instructions made in response to the comment(s) or a response, as appropriate. We have also indicated if the form was completed by a team applying the framework during a systematic review (SR) or applying the framework retrospectively during a future research needs project (FRN).

**Summary Table (n, %)**

Question Number	Question Text	Number (n=8) No. (%)
Q5	<b>Stage sheet was completed</b> Systematic review Future research needs document Other	3 (37.5%) 5 (62.5%) 0 (0%)
Q7	<b>Who completed research gap framework worksheet</b> P.I. only Other investigator only Other investigator and Research staff member Research staff member only Other: team feedback	4 (50%) 1 (12.5%) 1(12.5%) 1(12.5%) 1 (12.5%)
Q8	<b>Previous gap identification</b> No Yes	0 (0%) 8 (100%)
Q10	<b>Advantages to using framework vs. previous gap identification method</b> No Yes	0 (0%) 8 (100%)
Q12	<b>Disadvantages to using framework vs. previous gap identification method:</b> No Yes	1 (12.5%) 7 (87.5%)
Q14	<b>Problems or issues when using framework vs. previous gap identification method:</b> No Yes	2 (25%) 5 (62.5%) 1 (12.5%) no answer
Q16	<b>Suggestions to improve framework sheet efficiency/usefulness:</b> No Yes	3 (37.5%) 5 (62.5%)
Q18	<b>Suggestions to improve framework sheet instructions:</b> No Yes	5 (62.5%) 2 (25%) 1 (12.5%) no answer

## Q9. Describe previous gap identification method

Form	Stage Completed	Description of Gap Identification Method
A	FRN	<XXX>; A Future Research Needs report was also undertaken to systematically prioritize research gaps in the areas of <XXX>, and to develop a list of research questions to address the prioritized gaps based on the systematic review.
B	FRN	Previously, we would review the comparative effectiveness report to determine the number of studies and quality (strength) of evidence to determine the potential research gaps. High quantity + high quality (no gap); high quality + low quantity (no gap);
C	SR	All our reports have a section that identifies gaps. The earlier reviews tended not to be organized around PICOTS.
D	SR	Future Research Needs for the <XXX>.
E	FRN	Have had other Future Research Needs Projects (Different Investigators)
F	FRN	<XXX> Future Research Needs report <XXX> Future Research Needs report Numerous systematic reviews
G	SR	I'm not sure what you mean by "identified gaps from systematic reviews". We regularly write a future research needs section but I'm not sure if these are the same thing.
H	FRN	Yes, this was our third FRN project in addition to the research gaps sections of prior reviews.

## Q11. Describe advantages of using framework

Form	Stage Completed	Description of Advantages
A	FRN	Facilitate the use of a systematic process to identify evidence gaps.
B	FRN	This framework provides standardized criteria to identify potential gaps in the literature, which was previously somewhat arbitrary.
C	SR	THE PICOTS framework assists writers in considering all areas.
D	SR	Systematic, transparent way; involvement of different stakeholder groups
E	FRN	The coding / having a list of reasons for the gaps is helpful; but we do not want this to be part of the protocol because we are not sure how to use it and what it adds to the process.
F	FRN	Requires you to be more systematic
G	SR	I can see advantages to using a framework such as this. Without a framework our approach has been fairly non-systematic and may be influenced by priorities of the research team or driven by what they see as the “most important” gaps.
H	FRN	Yes – a structured approach is helpful for constraining the content to researchable topics. It also helps to see where there are redundancies, and helps keep the research team focused on the scope of the project.

### Q13. Describe disadvantages of using framework

Form	Stage Completed	Description of Disadvantages	XXX Response
A	FRN	_____	_____
B	FRN	We found that applying this framework to all potential combinations of PICOS for the <XXX> FRN project yielded more than 1000 research gaps. This was due to the large number of populations, settings, and intervention/comparisons and the overall poor quality of the existing literature. The framework is much more practical when there is a manageable number of potential PICOS combinations (e.g. FRN for <XXX> project).	We have added text to the instructions suggesting that teams discuss prior to the use of the framework whether to, and how to, lump or split. For instance, it may be more manageable to abstract gaps by class of intervention and comparison.
C	SR	The overlap with GRADE is less helpful as it is not clear how the gap will assist in the judgments of the SOE. For example a gap in research design....not all issues can be addressed with trials....so not sure how to make this link. Also I think the list of reasons for developing a gap should be expanded. I found I used B2 very often to provide a reason for the gap....and the recommendations are widely varied. Thus some categories are not discriminating enough.	We did not consider the process of identifying gaps as a way to assist in making judgments about SOE. The framework was designed to leverage work completed, if SOE was assessed. We do not see how B2 could be made more specific. It is to be selected if the body of evidence was considered at high risk of bias (this may be for a number of reasons, but is aggregated across the studies).
D	SR	Involvement of different stakeholder groups may be not representative; information about ongoing studies may be incomplete ; no full representation of the NIH, other funding agencies; the role of industry is unclear	We have clarified at the beginning of the instructions the purpose for the framework – to identify and characterize gaps from systematic reviews. How to solicit stakeholder involvement and prioritize gaps is beyond the scope of this work.
E	FRN	The gaps are not clearly conveyed by the table. The statement in the instructions that “other elements will be apparent from the key question” does not seem to be accurate to us. At the FRN point it is almost too late; too difficult to use. It may have been more helpful during the CER.	We have added some discussion of this, including examples, under Characterization of Research Gaps in the instructions. We agree that there are different challenges in applying the framework retrospectively versus while completing a systematic review.

Form	Stage Completed	Description of Disadvantages	XXX Response
			We have added text in instructions providing some suggestions about how to proceed if doing so retrospectively.
F	FRN	<p>Not all gaps are equally important, so it is not an efficient use of time to be required to complete this chart for every gap. Suggest that only the critical research gaps be prioritized for the chart.</p> <p>It may be too cumbersome for readers to understand. Many of the codes may need to be listed for each gap. It is not clear that using the codes, as opposed to a narrative description, will make the gaps easier or more efficient to understand.</p>	<p>It is unclear how one would determine the ‘most critical’ gaps without first systematically identifying and characterizing the gaps, such as through use of this framework or other method.</p> <p>The codes and worksheet were developed to aid in abstraction. The future research needs section of the systematic review, or future research needs document, would present the gaps. Our previous report provided a suggested presentation format (also another EPC has produced a report on how to present gaps).</p>
G	SR	<p>The key disadvantage I see is that it may replicate work already done. This may be less of an issue if it was done alongside preparing the results, as was suggested in your instructions. I did it after the review was complete so I found it fairly redundant, as much of this information was already in SOE or summary tables.</p> <p>I’m not sure that it highlighted any issues that were not already known, i.e., very few studies providing data for the same comparisons &amp; outcomes. So it could add a lot of work without providing much additional insight.</p>	<p>We would hope that a team could leverage the work done in completing SOE but we take your point that it could also be redundant. We think this will depend on the team, the specific review, and the timing of applying the framework.</p>
H	FRN	<p>To some degree it can be overly constraining and it really doesn’t work well for a review topic on which there is very little available. In this case, the overwhelming gap is that much more research needs to be done, period. Trying to specify at the level of the framework is not yet possible or appropriate. Also, the framework is not ideal for methodologic issues.</p>	<p>We agree that the framework may be too granular to use for questions for which, essentially, the entire question is a gap. We have added some text about these sorts of decisions to the instructions</p>

**Q15. Describe problems or issues faced when using framework**

Form	Stage Completed	Description of Problems or Issues	XXX Response
A	FRN	_____	_____
B	FRN	The only problem is the same as the disadvantage.	See above.
C	SR	I wasn't sure what would be helpful to you in the free text and notes.	We have added text addressing these sections on the worksheet.
D	SR	Complicated, does not address strength of existing evidence	We feel that the strength of existing evidence is explicitly considered in the reasons for gaps. Further, we have tried to link the reasons for gaps with the various domains used in different systems to rate the strength of existing evidence.
E	FRN	Not sure the table format adds much value to the process. Seems like we would have to shoe horn items into the table and get little added value from the exercise. Not sure how to complete the PICOTS sections for the types of gaps we identified.	We are not sure of current process used by this EPC team (Q9), so do not have a basis for responding to how use of the framework to identify research gaps in a systematic manner might add value. We have added text to the instructions to clarify characterization of research gaps using PICOS elements in worksheet.
F	FRN	_____	_____

Form	Stage Completed	Description of Problems or Issues	XXX Response
G	SR	<p>For the review I used, we had many, many comparisons (22 drug-drug comparisons for two different conditions within each of 5 key questions) and many outcomes within each of the questions; for many comparisons and outcomes there were very few studies. Therefore, I found the framework rather cumbersome to use.</p> <p>The other challenge was when the outcomes weren't graded. Within the review I used, we only graded outcomes for 2 of the key questions, so for the outcomes (which were numerous) within the other key questions, we had no SOE assessments. So then the reason for gaps was usually A1 (no studies) or A2 (limited number of studies).</p>	<p>We have added to the instructions a discussion of lumping/splitting which, we think, would help in the situation described.</p> <p>We added to instructions decision about whether to review all questions and outcomes, even if not 'graded'.</p>
H	FRN	<p>See question above – it worked for the review in question (&lt;XXX&gt;), but not for another review (&lt;XXX&gt;) that started from all insufficient.</p>	<p>We agree that the framework may be too granular to use for questions for which, essentially, the entire question is a gap. We have added some text about these sorts of decisions to the instructions</p>

## Q17. Suggestions for improving usefulness and efficiency of framework

Form	Stage Completed	Suggestions to Improve Framework	XXX Response
A	FRN	_____	_____
B	FRN	This framework is designed very well for specific projects that contain a manageable number of research gaps. However, for the <XXX> FRN project where literally every combination was determined to be a research gap. It would be impossible to ask expert Stakeholders to evaluate such a large number of research gaps and to then build consensus on prioritization. As exemplified in this project, I do not believe this tool is appropriate for use in all FRN projects and use should be determined on a case-by-case basis by discussion between the investigative team and the TOO.	We have clarified at the beginning of instructions where we envision this framework fitting within the work of a systematic review and future research needs project. We have added text describing decisions to be made about which questions and outcomes to consider (only those assessed for strength of evidence?) and dealing with multiple interventions/comparisons (lumping versus splitting).
C	SR	Might be easier to complete in an excel sheet where some responses can be constrained.	We agree. We completed abstraction for this project using forms in Distiller. We have added a note about this option in the instructions.
D	SR	Research and development framework (used by industry) can be applied using complete information about completed and ongoing studies ; electronic surveys of the representative groups of sponsoring organizations; policy makers, researchers, and consumers (NO “patients”); survey should address group specific interests (implications for funding, research methodology, policy, consumer interests)	We think these comments relate to other aspects of developing a research agenda and are beyond the scope of this project.
E	FRN	If we are going to have a table, it might be more useful to state the gap, then code the reason and the PICOTS issues. I am not sure how the table format is supposed to aid in either making conclusions or communicating them to readers. What is most important? Having gaps with the same reason? Having gaps related to a PICOTS element? Is the table supposed to help you summarize across gaps?	The worksheet was designed to aid in identification of research gaps. The future research needs section of the systematic review, or future research needs document, would present the gaps. Our previous report provided a

Form	Stage Completed	Suggestions to Improve Framework	XXX Response
			suggested presentation format (also another EPC has produced a report on how to present gaps).
F	FRN	Do not think it is necessary to have a separate chart for each key question Instead of “serial number” suggest calling it “gap number”	The gaps are abstracted by question, and characterized by listing the elements of PICOS from the question where evidence is inadequate. Because of this explicit link to questions, each review question should have a worksheet. The alternative is to use the PICOS to flesh out the entire research question needed to address the gap. We have changed the column header to “gap number”.
G	SR	As I have alluded to above, it will likely be most efficient to incorporate it at an early stage in the review. It may also be most efficient to focus on some key comparisons or questions or outcomes. Since you mention using the SOE information, should it be based on or driven by the “graded” outcomes?	We have added text about applying the framework retrospectively versus during completion of a systematic review. We have added text to instructions suggesting team make decision about whether to limit consideration and abstraction of gaps to those questions and outcomes that were assessed for strength of evidence.
H	FRN	_____	_____

### Q19. Suggestions for improving framework instructions

Form	Stage Completed	Suggestions for Improving Instructions	XXX Response
A	FRN	_____	_____
B	FRN	The instructions were extremely clear.	Thank you.
C	SR	_____	_____
D	SR	Depends on the changes in the research and development framework	
E	FRN	Provide one or two examples of a completed table. Describe how the table can or should be used and clarify what the purpose is.	We have provided, embedded in instructions, some examples to illustrate specific points. We have appended to end of instructions an example of a completed sheet.
F	FRN	_____	_____
G	SR	I found the instructions clear. As I mentioned above, many of the comparisons and outcomes were not graded, therefore the instructions “Work completed in grading the body of evidence should be used in completing this worksheet” are not relevant. What do we do when grading has not been done?	We have revised the text in this section to address this question.
H	FRN	_____	_____

# APPENDIX E

XXX EPC Frameworks Project: Research Gaps Worksheet  
 Systematic Review ID: \_\_\_\_\_

Completed by – \_\_\_\_\_

Date – \_\_\_\_\_

Page \_\_\_\_ of \_\_\_\_

Key Question Number (Enter "99" if outside scope) – \_\_\_\_\_

Gap No.	Reason(s) for Gap*	Other Reason(s) for Gap	POPULATION (P)	INTERVENTION (I)	COMPARISON (C)	OUTCOMES (O)	SETTING (S)	Free Text Gap	Notes

**\* Reasons for Gap**

**Insufficient or Imprecise Information** → **A1**=No studies, **A2**=Limited number of studies, **A3**=Sample sizes too small, **A4**=Estimate of effect is imprecise

**Information at Risk of Bias** → **B1**=Inappropriate study design, **B2**=Major methodological limitations in studies

**Inconsistency or Unknown Consistency** → **C1**=Consistency unknown (only 1 study), **C2**=Inconsistent results across studies

**Not the right information** → **D1**=Results not applicable to population of interest, **D2**=Inadequate duration of interventions/comparisons, **D3**=Inadequate duration of follow-up,

**D4**=Optimal/most important outcomes not addressed, **D5**=Results not applicable to setting of interest

## Instructions for research gaps framework 23 July 2012

### Purpose

A *research gap* is a topic or area for which missing or inadequate information limits the ability of reviewers to reach a conclusion on a given question.

The *framework*, and accompanying worksheet, is designed to facilitate an explicit process for the identification, description and organization of research gaps during systematic reviews.

When completed during the completion of a systematic review, we suggest that review authors fill out this worksheet soon after the data synthesis phase, while in the process of writing the results section. The results would be used by the team in developing the future research needs section of the report of the systematic review.

The framework may also be applied retrospectively, that is, to identify and characterize gaps from an existing systematic review. For instance, within the Evidence-based Practice Center (EPC) program, the framework may be completed at the start of a Future Research Needs (FRN) project using an existing systematic review that may or may not have been completed by the same team. When completing the framework retrospectively, restrict abstraction of gaps and reason(s) for gaps to explicit statements made by the review authors. Do not review and interpret the specific results to identify gaps or reasons for gaps. Abstract the gaps and reasons for gaps that are specifically noted by the systematic reviewer authors. The team completing the abstraction retrospectively should meet to discuss and agree on sections to be reviewed (text, tables, etc.) as well as what to do if there are apparent discrepancies between sections of the systematic review. Inserting the section name and page number(s) (in Notes field of framework worksheet) used to identify a gap might be helpful for adjudication and review. For an FRN, the gaps identified would be used by the team in developing the list of gaps to be presented to and considered by stakeholders (i.e., gaps may be prioritized or categorized prior to presentation to stakeholders).

There are a number of decisions that a team using the framework should discuss prior to starting the gap identification process. The decisions will be influenced by the purpose for the identification of the gaps:

- At what point will the framework be applied: during completion of a systematic review or retrospectively? We have included guidance for different stages but suggest the optimal time of use is during the writing of the results section of a systematic review.
- Will all questions and outcomes be reviewed for gaps? The team could decide to limit identification to those questions and outcomes for which strength of evidence was assessed (see page 2).
- What level of granularity is needed for the characterization of the gaps? The team should discuss whether to lump or split concepts and, if lumping, how that would be done (see page 6).

### Instructions for use of worksheet

1. As required, enter the name of EPC report or systematic review project in upper left hand corner.
2. Complete one or more worksheets for each review question (question included in the systematic review). Indicate question number in top right hand corner. (Enter “99” if gap is outside scope of original systematic review questions.)
3. Initial and date each worksheet.
4. Number the worksheets.
5. Enter gaps into the worksheet, per guidance provided below. In the worksheet table, each row is one research gap and is numbered accordingly (“Gap Number”).

Note: The worksheet is provided as a word processing document but it may be translated for use on web-based systems, databases, or spreadsheets.

### Guidance for completing worksheet

#### **Coding for the Reason(s) for Research Gaps**

Enter the reason(s) for the gap in the second column. The classification of the reasons for gaps are listed and coded in the footnote of the gaps abstraction worksheet. Choose the most important reason(s) for the existence of the research gap. The reason selected should be the reason(s) that most precludes conclusions from being made about that question. In other words, consider what would be needed to allow for conclusions to be made. If that particular reason(s) for gap was resolved, could the reviewer draw a conclusion about the question? Codes for more than one reason may be entered in this column, as appropriate. Reasons that cannot be fit within the defined coding system should be listed in the third column titled “Other Reason(s) for Gap”.

The reasons for gap are categorized as:

- A. Insufficient or imprecise information
- B. Information at risk of bias
- C. Inconsistency or unknown consistency
- D. Not the right information

For each of these categories, the relevant domain or element from the EPC Strength of Evidence (SOE), GRADE and USPSTF grading systems are listed. It may be useful to review the most recent guidance about each of these evidence grading systems. Work completed in grading the body of evidence may be leveraged in completing this worksheet. The concepts discussed below should be considered and applied in cases where SOE was not assessed. Decide before starting process if all questions and outcomes will be reviewed for gap identification, or only those which were considered in a strength of evidence assessment.

The specific reasons for gaps are listed in the footnote of the worksheet and described below:

A. Insufficient or imprecise information

Information is insufficient or imprecise if data are sparse and thus uninformative and/or confidence intervals are wide and thus can include conflicting results or conclusions.

A1 – This reason should be selected if no studies are identified.

A2 – This reason should be selected if a limited number of studies are identified.

A3 – This reason should be selected if the sample sizes or event rates in the available studies are too small to allow conclusions.

A4 – This reason should be selected if the estimate of the effect (such as achieved from a meta-analysis) is imprecise. That is, if the width of the confidence interval is such that the conclusion could be for benefit or harm.

Note: It would be inconsistent to choose Reason A1 (no studies) and Reason A2 (a limited number of studies) to describe the same gap, since only one or the other can be true. Likewise, Reasons A3 and A4 would not occur at same time as Reason A1.

Correspondence to grading systems:

- *EPC SOE*: **Precision** is a required domain.
- *GRADE*: The GRADE Working Group advises decreasing the grade of the quality of the evidence if the data are “**imprecise** or sparse”.
- *USPSTF*: The following questions are considered while grading the evidence:
  - “How many studies have been conducted that address the key question(s)?”
  - “How large are the studies? (i.e., what is the precision of the evidence?)”

B. Information at risk of bias

The aggregate risk of bias is contingent upon the risk of bias of the individual studies.

B1 – This reason should be selected if the study design(s) are inappropriate to address the question of interest (e.g., non-randomized studies for question where randomized studies are more appropriate).

B2 – This reason should be selected if there are major methodological limitations to the available studies leading to high risk of bias or limited internal validity.

Correspondence to grading systems:

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

C. Inconsistency or unknown consistency

Consistency is the degree to which results from included studies appear to be similar or in concordance.

- C1 – This reason should be selected if only one study is identified. If there is only one available study, even if considered a large sample size, the consistency of results is unknown.
- C2 – This reason should be selected if the results from available studies are inconsistent. Elements to consider include whether effect sizes vary widely, if the range of effect sizes is wide, limited or no overlap of confidence intervals, and, as appropriate, if statistical tests, such as  $I^2$ , indicate heterogeneity.

Note: It would be inconsistent to choose Reason C1 and Reason C2 to describe the same gap, since only one or the other of these reasons can be true.

Correspondence to grading systems:

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

D. Not the right information

There are a number of reasons why identified studies might not provide the right information to make conclusions about the review question.

- D1 – This reason should be selected if the results from studies might not be applicable to the population of interest.
- D2 – This reason should be selected if the duration of the interventions and/or comparisons is considered too short.
- D3 – This reason should be selected if participants are not followed up for long enough duration in the included studies.
- D4 – This reason should be selected if the optimal and/or most important outcomes are not assessed in the included studies. This reason also includes instances where only data on surrogate outcomes are available while data on more clinical and/or patient-important outcomes are needed.
- D5 – This reason should be selected if the results from studies might not be applicable to the setting of interest. This would include cases where the interventions assessed in the studies are not applicable or available in setting of interest.

Correspondence to grading systems:

- *EPC SOE*: **Directness** is a required domain. It also incorporates the element of surrogate versus clinical outcomes.
- *GRADE*: **Directness** is a key element.
- *USPSTF*: The following question is considered while grading the evidence:
  - “To what extent are the results of the studies generalizable to the general US primary care population and situation? (i.e., what is the external validity?)”

## Characterization of Research Gaps

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

Population (P) – In this column, specify as much as possible about the age, sex, race/ethnicity, clinical stage, etc. of the population that is not adequately represented in the evidence base. However, research gaps often do not relate to any specific population but refer to the general population as outlined in the review question. In that case, it is not necessary to reiterate the population already described in the review question. For example, if the population described by the Key Question is ‘pregnant women’, there is no need to write ‘pregnant women’ in this column. This column is designed for other populations, aspects of populations, or subgroups that have not been adequately addressed by the evidence. If the population being studied was ‘pregnant women’, but none of the studies included pregnant teenagers, or pregnant women over the age of 45, or minority pregnant women, or pregnant women in underdeveloped countries—and the authors of the review consider this a gap—this information would be recorded in this column.

Intervention (I) – In this column, specify the name of the intervention that is inadequately included in the evidence base (generic names of drugs and devices are typically preferred), the duration of the intervention, its dose, its frequency, who will administer it, etc., as appropriate. As for the population, it may not always be appropriate to specify great detail about the intervention.

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

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

Setting (S) – In this column, when appropriate, specify the relevant settings or aspect of setting not adequately addressed in evidence base.

## Special Considerations

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

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

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

### Free Text Gap column

The Free Text Gap column may be used to characterize research gaps which are difficult to characterize using the PICOS framework. Interventions could potentially include a range of treatment options, order of treatment options, individualization of treatments, etc. These are often gaps for which it is difficult to identify a clear intervention or comparison of interest. It may not be possible to translate these gaps into appropriate research questions. Examples of questions derived from such research gaps are: “What are the optimal glucose thresholds for medication use in women with gestational diabetes?”; “In what order should patients with cystic fibrosis perform their airway clearance therapies?” and “How should physicians choose an airway clearance therapy for a given patient with cystic fibrosis?”

### Lumping Versus Splitting

A decision should be made prior to starting abstraction of gaps, either as part of a systematic review or retrospectively, as to how to deal with cases where there is little or no evidence across a broad question resulting in a very high number of comparisons and outcomes with gaps. For example, in such cases, a team may choose to lump together interventions of a certain type or simply note that the entire question is a gap. The team should also discuss and decide *a priori* whether gaps will generally be lumped or split, such as by classes of interventions or types of outcomes. This may depend on the type of question(s) addressed in the review and the purpose for identifying gaps (i.e., the need for granularity).

Example:

Option 1—Lumping or pooling outcomes with same reason for gap

<b>Reason for gap</b>	<b>P</b>	<b>I</b>	<b>C</b>	<b>O</b>	<b>S</b>
C2		Cognitive behavioral therapy		Pain, mood, and disability	

Option 2—Splitting or separating outcomes with same reason for gap

<b>Reason for gap</b>	<b>P</b>	<b>I</b>	<b>C</b>	<b>O</b>	<b>S</b>
C2		Cognitive behavioral therapy		Pain	
C2		Cognitive behavioral therapy		Mood	
C2		Cognitive behavioral therapy		Disability	

EXAMPLE completed worksheet  
**Research Gap Worksheet**  
**Project Name: Oral diabetes meds**

Completed by – KR  
 Date – 20 July 2012  
 Page 1 of 1  
 Key Question Number – 3

Serial No.	Reason(s) for Gap*	Other Reason(s) for Gap	POPULATION (P)	INTERVENTION (I)	COMPARISON (C)	OUTCOMES (O)	SETTING (S)	Free Tax Gap	Notes
Example	B1			Metformin	Metformin + Any insulin	Weight, lipoproteins	-		-
Example	D1		African-American adults						
Example	A3, A4			Sulfonylurea	GLP-1 agonist	HDL			
Example	D1, D4		Over 70 with comorbidities			Hypoglycemia, liver injury, congestive heart failure			

**\* Reasons for Gap**

**Insufficient or Imprecise Information** → A1=No studies, A2=Limited number of studies, A3=Sample sizes too small, A4=Estimate of effect is imprecise

**Biased Information** → B1=Inappropriate study design, B2=Major methodological limitations in studies

**Inconsistency or Unknown Consistency** → C1=Consistency unknown (only 1 study), C2=Inconsistent results across studies

**Not the right information** → D1=Results not applicable to population of interest, D2=Inadequate duration of interventions/comparisons, D3=Inadequate duration of follow-up, D4=Optimal/most important outcomes not addressed, D5=Results not applicable to setting of interest