

Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009)

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov
Contract No.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an already-established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/purpose.

AHRQ expects that Comparative Effectiveness Reviews will be helpful not only to government programs but also to individual health plans, providers, and purchasers, and to the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that the greatest range of decisionmakers possible (and that includes consumers who make decisions about their own and their family's health) can benefit from the evidence. Work under this program is transparent and user driven. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

Acknowledgements

The Southern California Evidence-based Practice Center at RAND would like to acknowledge with appreciation the guidance of Beth Collins-Sharp and Supriya Janakiraman at AHRQ, Rose Campbell at Oregon Health Sciences Center, and the invaluable contributions of the technical experts who assisted with the assessments.

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Background

The Effective Health Care Program (EHC) researches available health care tests and treatments to determine whether there are significant advantages or disadvantages with different approaches. The results of this comparative effectiveness research can help people make better decisions about what health care they want to have, and can help clinicians and health care purchasers to focus on the best tests and treatments. Initial work in this program originates from Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003. Section 1013 authorizes AHRQ to conduct and support research with a focus on outcomes, comparative clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services. The Effective Health Care Program follows three approaches to research in order to provide current, unbiased evidence on health care interventions.

- Review and synthesize published and unpublished scientific evidence.
- Promote and generate new scientific evidence and analytic tools.
- Compile the findings and translate them into a variety of useful formats for stakeholders.

Systematic reviews by the Evidence-based Practice Centers (EPC) Program contribute to the first area of the EHC Program. EPC research reviews provide comprehensive appraisal and synthesis of evidence following explicit methodological criteria.

A Comparative Effectiveness Review (CER) is a unique type of systematic review, which synthesizes the available scientific evidence on a specific topic. CERs expand the scope of a typical systematic review, which focuses on the effectiveness of a single intervention, by comparing the relative benefits and harms among a range of available treatments or interventions for a given condition. In doing so, CERs more closely parallel the decisions facing clinicians, patients and policymakers, who must choose among a variety of alternatives in making diagnostic, treatment, and health care delivery decisions.

In choosing topics for CERs, a number of criteria are considered including the burden of illness; evidence suggesting underuse or overuse; the cost of the intervention or of not treating the illness; controversy surrounding the treatment; and interventions intended to treat conditions that disproportionately affected women, traditionally underserved minorities, and the elderly (this group was subsequently expanded to include children). The first 14 CERs were conducted from 2005 through 2007. The topics and completion dates are shown in Table 1.

AHRQ recognizes that periodic assessments of the evidence base supporting each of the comparative effectiveness reviews is an important and necessary part of the Effective Health Care (EHC) Program. The rapidity with which new research findings accumulate makes it imperative that the evidence be assessed periodically to determine the need for a full-scale update. The EHC Program, then, initiated concurrent and parallel work to address this need both methodologically and programmatically. The development of methods guidance for updating was initiated to inform the research of systematic reviewers. This methodologic guidance will supplement the EHC Methods Guide for Comparative Effectiveness Reviews (www.effectivehealthcare.gov). In parallel with the methods effort, an initial, rapid program assessment was commissioned to assess the need for the findings of the CERs completed to that point to be updated. The Southern California Evidence-based Practice Center (SCEPC) was tasked with conducting this assessment. Findings from the assessment were presented to AHRQ for consideration within the usual program criteria to prioritize the topics for updating within the EHC Program. This document presents the findings from the assessment for public information and transparency.

The assessment of the evidence base included the following questions and other consideration depending on the topic of the comparative effectiveness review.

- Have new medications, procedures, or devices been introduced?
- Have the existing medications, procedures, or devices been approved for new indications?
- Have any new advisories or alerts been issued?
- Has there been a change in scope (e.g., new patient populations, new outcomes)?
- Is there new evidence from new studies or studies that were incomplete at the time of the existing report?
- Have new methodologies been introduced (e.g., new statistical techniques or significant changes in the Comparative Effectiveness Review Methodology Guide)?

Table 1. Topics of Initial CERs

Report Number and Title	Publication
1. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease	12/2005
2. Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities	02/2006
3. Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment	05/2006
4. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis	09/2006
5. Comparative Management Strategies for Renal Artery Stenosis*	10/2006
6. Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotic	01/2007
7. Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression	01/2007
8. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes*	07/2007
9. Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease	10/2007
10. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension	11/2007
11. Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults	11/2007
12. Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis	12/2007
13. Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer	02/2008
14. Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes [#]	09/15/08
* AHRQ decided to update this report; thus, it was not considered in this report.	

#This report was completed too recently for consideration.

Methods

Changes in the evidence underlying clinical guidelines and standards of care, i.e., contradictory or even confirming evidence from large well-designed studies published subsequent to the original systematic review, can have significant implications for those guidelines and for clinical and consumer decision-making. The rapidity with which new research findings accumulate makes it imperative that the evidence be assessed periodically to determine the need for a full-scale update. In early 2008, AHRQ determined that in order to meet their intended objectives the EHC Program should assess the need for the findings of the CERs completed to that point to be updated. The Southern California Evidence-based Practice Center (SCEPC) was tasked with conducting this assessment, that is, reviewing the literature and gathering expert opinion in support of this assessment.

The science of updating systematic reviews has been developing for the past decade. Prior to 2001, no method or criteria existed to determine whether evidence-based products remained valid or whether the evidence underlying them had been superseded by newer work. In the late 1990s, AHRQ asked the SCEPC to determine whether their clinical practice guidelines needed to be updated and how quickly guidelines go out of date. The SCEPC first devised a conceptual model that consisted of six situations that would require a guideline to be updated or withdrawn (Shekelle et al., 2001). These situations included changes in (1) the available interventions, (2) the evidence on the benefits and harms of existing interventions, (3) the outcomes that are considered important, (4) the evidence that current practice is optimal, (5) the values placed on outcomes, and (6) the resources available for health care. Their assessment of the need to update the AHRQ guidelines did not take the final two situations into account as the measurement of these situations was considered beyond the scope of the process. The mandate also required that, rather than conducting a series of new systematic reviews, the SCEPC would devise a method that could be feasibly applied to a large number of guidelines. Reasoning that any new findings that differed from the previous findings with sufficient magnitude to warrant reconsideration of a guideline would be both published in a major journal and familiar to experts in the field, they thus used a combination of a focused literature search and the guidance of experts from relevant disciplines as a more pragmatic way to help identify potentially significant new evidence. Using this approach, they determined that out of 17 guidelines, new evidence and expert assessment indicated that 7 required a major update; 6 were found to be in need of a minor update; 3 were assessed as still valid; and for 1 guideline, no conclusion could be reached. Survival analysis indicated that about half the guidelines were outdated in 5.8 years; at 3.6 years, no more than 90 percent of the guidelines were still valid. (Shekelle et al, 2001)

The Cochrane Collaboration has striven to update its systematic reviews biennially. However, such updates involve a huge investment of time and effort and might not be appropriate for all topics. Thus, in 2005, members of the Collaboration assessed whether 4-year updates might be adequate for some topics by comparing the results and conclusions of 1998 reviews with their 2002 updates. Among 254 updated reviews, only 23 (9%) had a change in conclusion, supporting the idea that a priority approach, rather than an automatic time-based approach, should be used to determine the need for an update (French et al., 2005).

Shojania and colleagues also devised a method—using survival analysis—to assess the need to update reviews and tested it among 100 meta-analyses published from 1995 to 2005. The method did not involve expert assessment, but instead relied on a combination of quantitative and qualitative analysis. The quantitative signal that a review was out-of-date was a change in statistical significance or relative effect size of at least 50 percent. Qualitative signals included major changes in the

characterization of effectiveness, new information about adverse events, or some other warning about the reliability of previous findings. Among the 100 reviews (which ranged in age from approximately 1 to 10 years), 57% showed some sign of being out-of-date. The median length of survival without displaying such a signal was 5.5 years; although 7 percent of the reviews were out-of-date by the time they were published, only 4% were out of date within a year of the end of the search period. Thus, like the Shekelle study, this study showed the need for frequent, and in some cases almost immediate, updating. The apparent need for more frequent update was related to topic and to heterogeneity in the original report.

To compare the comprehensiveness and effort required to employ the SCEPC abbreviated method with that of a typical full-blown literature search, Gartlehner and colleagues (2004) at the University of North Carolina Chapel Hill and RTI first created a streamlined version of the SCEPC method. They then employed both to assess the need to update the 1996 US Preventive Services Task Force Guide to Clinical Preventive Services. The study found that although the abbreviated SCEPC method identified fewer eligible studies than the “traditional approach,” Task Force members who were acting as project liaisons rated none of the studies missed by the abbreviated method as important to assessing the need for an update to the guidelines. Thus they deemed the revised approach to be an efficient and acceptable method for assessing the need to update a guideline.

Assessment of Need to Update CERs

To assess the need for the first set of effectiveness reviews to be updated, the SCEPC employed a modification of a method devised by Shekelle and colleagues (Shekelle et al, 2001) to conduct an abbreviated review of the literature. The process relied on a combination of expert opinion, and limited search and review of the peer reviewed literature and the Federal Food and Drug Administration (FDA) website (MedWatch Database) to assess whether a CER needs to be updated. The methodology was applied to each CER separately and independently.

Expert Consultation

Based on our earlier work (Shekelle et al, 2001), we drafted a brief letter that posed two questions about each conclusion reached in the original reports. The letter incorporated an introduction to the study, the original key questions, the conclusions corresponding to those questions, and our questions regarding updating, and it asked the experts to offer their opinion as to whether the conclusion was still valid or was possibly, probably, or definitely in need of updating (Figure 1).

Figure 1. Sample Letter Excerpt (for Key Question 1 from CER#1)

<i>Conclusions from CER Executive Summary</i>	<i>Is this conclusion almost certainly still supported by the evidence</i>	<i>Has there been new evidence that may change this conclusion?</i>	<i>Do Not Know</i>
Key Question 1: What is the evidence of the comparative effectiveness of medical, surgical, and endoscopic treatments for improving objective and subjective outcomes in patients with chronic GERD?			
Medical therapy with PPIs and surgery (fundoplication) appeared to be similarly effective for improving symptoms and decreasing esophageal acid exposure.	Yes/No	Yes/No	Yes/No

<p>10 percent to 65 percent of surgical patients still require medications.</p> <p>The limited data available did not support a significant benefit of fundoplication compared with medical therapy for preventing Barrett's esophagus or esophageal adenocarcinoma.</p>			
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We conducted pilot tests of the initial letter among the principal investigator and several Technical Expert Panel (TEP) members for CER #12 (Therapies for Low Bone Density) as well as with the subject matter expert for CER #6 (Offlabel Uses of Atypical Antipsychotics), both of which were conducted by the SCEPC.

Based on the method used in our earlier report as well as the method of Gartlehner and colleagues (2004), we sought to include opinions from a minimum of 4 experts on each report topic, including that of the director of the EPC that conducted the original report (or the project leader, if it was not the EPC director). We contacted each of the EPC directors by express mail, asking them to provide their assessments of the need to update their reports (that is, the relevance of the conclusions) using the letter described above. We also asked for the names of at least three TEP members whom they believed were in a position to comment on the need for an update. We then contacted each of these experts to ask their participation. For reports for which no TEP had been appointed, we asked for the names of, and contacted, peer reviewers of the original report or other subject matter experts in the respective fields. If the PI failed to respond or could not recommend experts, we consulted relevant experts who had worked with the SCEPC on other projects. Experts who responded were sent the letter that incorporated key questions and conclusions for the report in question. Each respondent was offered an honorarium of \$100. The experts' responses were entered into an Excel spreadsheet. These responses were later summarized along with the findings of the literature searches (see below).

Literature Searches

We followed the method employed by Shekelle and colleagues for their assessment of the need to update the AHRQ Clinical Practice Guidelines. This method employed an abbreviated literature search strategy that focused on five major general-interest medical journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, The Lancet, and New England Journal of Medicine) supplemented with a small number of specialty journals tailored to each topic, as recommended by content experts (Shekelle et al, 2001) or, in a small number of cases, those most frequently cited in the original CER. The starting dates for searches were purposely set at one to two years prior to the ending dates of the original searches to capture any studies not included in the original searches.

With the exception of the literature searches conducted for reports #6 and 7, the title lists that resulted from all remaining literature searches were screened by a single member of the SCEPC staff or a subject matter expert (with prior EPC experience); the title lists for reports #6 and 7 were dually screened to ensure general agreement among reviewers. Abstracts were obtained for titles that appeared relevant, and the abstracts were further screened for inclusion. Inclusion/exclusion criteria were flexible: The only factors considered were whether the study being reported was relevant to one of the key questions/conclusions and whether the design consisted of a controlled trial or large observational study (systematic reviews were also included).

Added to the results of the searches were any articles cited or recommended by the experts and not already identified in our searches.

For each included report, study conditions, outcomes, and findings were abstracted to an evidence table. When necessary, full text articles were obtained to abstract information not found in abstracts.

FDA MedWatch and Canadian Health Services Database Searches:

To supplement our searches of the peer-reviewed literature, the Scientific Resource Center (SRC) at Oregon Health Sciences University (OHSU) searched the FDA MedWatch database and the Canadian Health Services (CHS) pharmaceutical database for any reports about drugs considered in the original CERs that were issued since (or 1 to 2 years prior to) the searches conducted for the original CERs.

Compilation of Findings

For each CER, we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA or CHS reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used a 4-category scheme:

- Original conclusion is still valid and this portion of the CER does not need updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is probably out of date and this portion of the CER may need updating
- Original conclusion is out of date

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.

If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

We then also assessed each CER as a whole regarding the need for updating. Each CER consists of multiple conclusions. In all cases we assessed, there was none in which all conclusions were assessed “still valid” or “possibly / probably out of date.” Hence, a conclusion was made regarding which CERs are most in need of updating now. Recognizing that resources are likely limited, we did not judge the presence of any individual conclusion that was “possibly out of date” as a necessary reason to update the entire CER. Rather we made our decisions based on the following considerations:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

Results and Conclusion

For each CER, we constructed summary tables that presented the evidence from the new searches, the expert responses, and an assessment regarding the need to update each conclusion. A summary of our findings is presented in Tables 2 and 3. In Table 2, we list the CER title and the number of conclusions assessed to still be valid. We also present the numbers of conclusions that are possibly or probably out of date, and definitely out of date, as well as the identification of potential safety issues and whether new evidence suggests a new indication for a treatment or a new treatment for an existing indication. Our overall assessment of the need for updating is shown in Table 3.

This report is accompanied by three appendixes. Appendix I presents the findings of our searches of the literature, FDA MedWatch Database and expert assessments, along with our overall recommendation regarding updating for each of the CERs assessed, and the conclusion(s) on which each recommendation is based. Appendix II presents the evidence tables, and Appendix III presents the literature search strategies for each CER topic.

Table 2. Summary of Assessments

CER Title	Number of conclusions assessed				Safety issue?	New indication for existing or new treatment
	Still valid	Possibly out of date	Probably out of date	Out of date		
Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease	6	1	1	4	Yes	Yes
Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities	1	2	1	0	No	Yes
Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer	2	3	2	1	Yes	No

CER Title	Number of conclusions assessed				Safety issue?	New indication for existing or new treatment
	Still valid	Possibly out of date	Probably out of date	Out of date		
Treatment						
Comparative Effectiveness and Safety of Analgesics for Osteoarthritis	20	4	1	2	Yes	No
Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics	16	4	1	0	No	Yes
Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression	13	7	0	0	No	No
Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease	13	5	1	0	No	No
Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension	7	1	0	0	No	No

CER Title	Number of conclusions assessed				Safety issue?	New indication for existing or new treatment
	Still valid	Possibly out of date	Probably out of date	Out of date		
Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults	14	4	1	1	No	Yes
Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis	35	4	0	0	No	Yes
Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer	10	7	3	0	No	No

Table 3. Assessments Concerning Need for Updating Reports

High Priority

- Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease
- Effectiveness of Noninvasive Diagnostic Tests for Breast Abnormalities
- Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment
- Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

Medium Priority

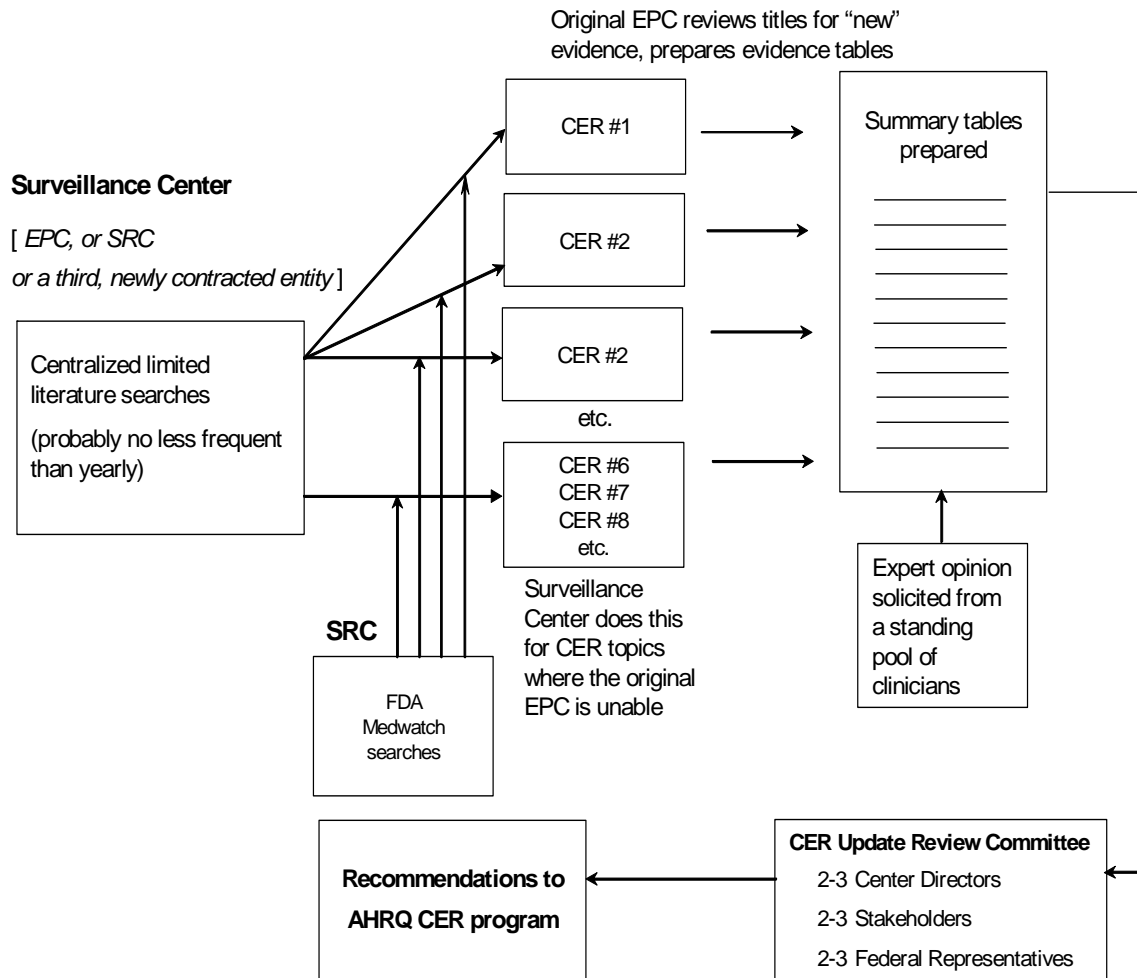
- Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics
- Comparative Effectiveness of Treatments To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis
- Comparative Effectiveness of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis in Adults
- Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

Low Priority

- Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression
- Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension
- Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease

We would envision a regular process of surveillance that is organized like Figure 2 below.

Figure 2 Proposed Process for Assessment of Need for CER Update



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Whitlock E. Challenges in Systematic Reviews— Can use Existing Reviews Save Time? Be Valid?
Presented at Annual EPC Meeting July 11, 2008