Methods Research Report

Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience

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This report is based on research conducted by the Southern California and University of Ottawa Evidence-based Practice Centers (EPCs) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10062-I [Southern California EPC] and 290-2007-10059-I [University of Ottawa EPC]). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Preface

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

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

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

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

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Surveillance and Identification of Signals for Updating Systematic Reviews: Implementation and Early Experience

Structured Abstract

Background. The question of how to determine when a systematic review needs to be updated is of considerable importance. Changes in the evidence can have significant implications for clinical practice guidelines and for clinical and consumer decision-making that depend on up-to-date systematic reviews as their foundation. Methods have been developed for assessing signals of the need for updating, but these methods have been applied only in studies designed to demonstrate and refine the methods , and not as an operational component of a program for systematic reviews.

Objectives. The Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice (EPC) program commissioned RAND's Southern Californian Evidence-based Practice Center (SCEPC) and University of Ottawa Evidence-based Practice Center (UOEPC), with assistance from the ECRI EPC, to develop and implement a surveillance process for quickly identifying Comparative Effectiveness Reviews (CERs) in need of updating.

Approach. We established a surveillance program that implemented and refined a process to assess the need for updating CERs. The process combined methods developed by the SCEPC and the UOEPC for prior projects on identifying signals for updating: an abbreviated literature search, abstraction of the study conditions and findings for each new included study, solicitation of expert judgments on the currency of the original conclusions, and an assessment of whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, on a conclusion-by-conclusion basis. Lastly, an overall summary assessment was made that classified each CER as being of high, medium, or low priority for updating. If a CER was deemed to be a low or medium priority for updating, the process would be repeated 6 months later; if the priority for updating was deemed high, the CER would be withdrawn from subsequent 6-month assessments.

Results and Conclusions. Between June 2011 and June 2012, we established a surveillance process and completed the evaluation of 14 CERs. Of the 14 CERs, 2 were classified as high priority, 3 as medium priority, and 9 as low priority. Of the 6 CERs released prior to 2010 (meaning over 18 months before the start of the program) 2 were judged high priority, 2 were judged medium priority, and 2 were judged low priority for updating. We have shown it is both useful and feasible to do such surveillance, in real time, across a program that produces a large number of systematic reviews on diverse topics.

Contents

Introduction

Background

The question of how to determine when a systematic review needs to be updated is of considerable importance. Changes in the evidence can have significant implications for clinical practice guidelines and for clinical and consumer decisionmaking, which depend on up-to-date systematic reviews as their foundation. The rapidity with which new research findings accumulate makes it imperative that the evidence be assessed periodically to determine the need for an update. Identifying updating signals would be particularly useful to inform stakeholders when new evidence is sufficient to consider updates of comparative effectiveness reviews (CERs).[1]

Systematic reviews are commonly updated at a preset time after publication.[2] For example, since 2002, the Cochrane Collaboration's policy has been to update Cochrane reviews every 2 years.[3] Such updates involve an investment of time and effort that may not be appropriate for all topics. In 2005, 254 Cochrane updates performed in 2002 were compared with the original reviews from 1998. Only 23 (9 percent) had a change in conclusion, which supports use of a priority approach, rather than an automatic time-based approach, to determine the need for an update.[4]

The science of identifying signals for updating systematic reviews has been developing for the past decade. Prior to 2001, no explicit methods or criteria existed to determine whether evidence-based products remained valid or whether the evidence underlying them had been superseded by newer work. Since the late 1990s, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) program has commissioned studies to develop methods to assess the need for updating evidence reviews. Two methods have been developed. First, the Southern California Evidence-based Practice Center (SCEPC), based at the RAND Corporation, conducted a study to determine whether AHRQ's clinical practice guidelines needed to be updated and how quickly guidelines go out of date. The SCEPC developed a method that combines expert opinion with an abbreviated search of the literature published since the original systematic review.[5,6] In 2008, the SCEPC adapted its method to assess the need for updating the CERs that had been prepared to that point (hereafter referred to as " the RAND method").[7] In parallel, a second method was devised at the University of Ottawa EPC (UOEPC). This method assessed the predictors of the need to update systematic reviews,[8] and was then tested using 100 meta-analyses published from 1995 to 2005.[9] The method did not involve external expert judgment, but instead relied on capturing a combination of quantitative and qualitative signals for the need to update a report (hereafter referred to as "the Ottawa method").

A series of subsequent methods projects led to the development of the Surveillance Program. In early 2008, AHRQ determined that to meet their intended objectives, the Effective Health Care Program should assess the need for the CERs completed to that point to be updated. The SCEPC was tasked with conducting this assessment. As part of this project, the SCEPC proposed a model for a program of regular surveillance for AHRQ CERs.[7]

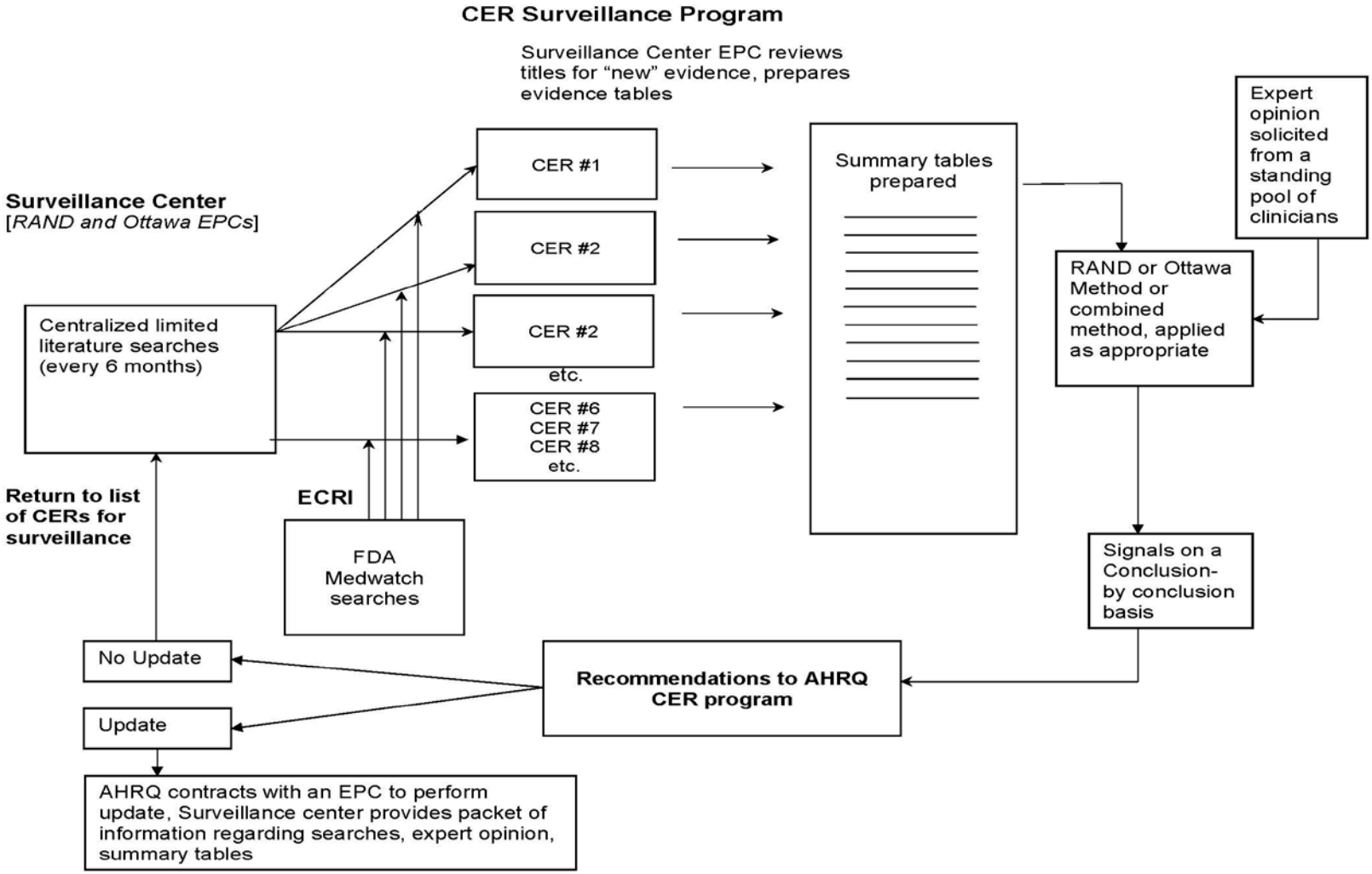
In 2010, AHRQ commissioned a pilot study to compare the results of the RAND and Ottawa methods for identifying signals for the need for updating. Chosen as test cases were three evidence reports on omega-3 fatty acids (omega-3 FA): the effectiveness of omega-3 FA for preventing and treating neurological disorders;[10] the effectivenesss of omega-3 FA for preventing and treating cancer;[11] and the effects of omega-3 FA on risk factors and intermediate

markers for cardiovascular disease.[12] The report concluded that the data support the use of either method, as, in general, they provide similar signals for the possible need to update systematic reviews.[13,14] Additionally, the report hypothesized that a hybrid model may offer advantages over either individual model.

AHRQ then commissioned the current Surveillance Program to evaluate 42 CERs using the RAND and/or Ottawa methods for identifying signals indicating the need for updating. Figure 1 is a diagram illustrating the overall process of the Surveillance program developed and conducted by the Ottawa and RAND EPCs.

In brief, 6 months after the release of a CER, the CER topic undergoes a limited literature search (five general medical journals and five specialty journals). The researchers conducting the assessment abstract any relevant studies into evidence tables. At the same time, a combination of local subject matter experts and experts from the original report (members of the Technical Expert Panel or Peer Review Panel) are contacted and asked to review the original conclusions and share their awareness of any new findings that might change a conclusion and therefore prompt an update. If the original report included meta-analyses, evidence for a quantitative signal will be sought in the new studies. The findings from the literature review and expert poll are combined in a summary table, and signals for the need to update are then determined on a conclusion-by-conclusion basis and for the CER as a whole. The EPCs then prepare a mini-assessment with the original conclusions, summary table, and evidence table, and their recommendation as to whether the priority for updating the CER is low, medium, or high. This determination is based on the number and types of conclusions deemed out of date.

Figure 1. CER surveillance program



AHRQ = Agency for Healthcare Research and Quality; CER = comparative effectiveness review; EPC = Evidence-based Practice Center; FDA = U.S. Food and Drug Administration

Methods

This report covers the period from June 2011 to June 2012 and is an interim analysis that summarizes the assessment of 14 CERs. The objective of the surveillance assessment system is to identify signals of the potential need for updating and not to conduct the actual update.

Identifying New Evidence From Published Studies

Search Strategy

The surveillance assessment system was designed to be implemented at 6 month intervals. The process starts with the assessment of a CER 6 months after its publication on the AHRQ Web site. The CERs determined to be up to date in the first cycle are reassessed 6 months after completion of the previous assessment. The CERs determined to be clearly out of date after the first assessment are not reassessed.

Starting with the search strategy employed in the original report, we conducted a limited literature search that included at least Medline/Pubmed and/or Cochrane, and, on a topic specific basis, additional databases. The search included five general medical interest journals (*Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet*, and the *New England Journal of Medicine*) and the specialty journals most relevant to that topic. The specialty journals were those most highly represented among the references from the original report. In general, we followed the search strategy from the original CER. However, we did make some modifications. For example, if we were aware of new drugs for the condition, their names were added to the search terms. Search inception dates were 6 to 12 months prior to the end date of the original CER search, in order to ensure overlap between the searches.

Study Selection and Abstraction

In general, we also used the same inclusion and exclusion criteria as the original CER. A single reviewer, experienced in systematic reviews, conducted a screening of the titles and abstracts and requested any articles deemed relevant to the topic. From those articles, a single reviewer extracted relevant data from articles that met the inclusion criteria and constructed an evidence table. These data included any study level details extracted in the original CER, e.g., sample size, study design, and outcomes measured, as well as the outcomes themselves.

Identifying New Evidence From the U.S. Food and Drug Administration, Health Canada, and Medicines and Healthcare Products Regulatory Agency (MHRA) (UK)

At monthly intervals, the ECRI EPC, under contract with AHRQ, monitored the U.S. Food and Drug Administration (FDA MedWatch), Health Canada, and MHRA Web sites for any new regulatory information or safety alerts about drugs relevant to the CERs under review. This information was forwarded to the SCEPC or UOEPC as appropriate and included in the final summary tables if deemed relevant. Appendix B outlines the methods the ECRI EPC used.

Identifying New Evidence From Experts and Expert Opinion

For each topic, a questionnaire matrix that listed the Key Questions and conclusions from the original executive summary was created. The matrix was sent to experts in the field, including the original project leader, technical expert panel members, and peer reviewers. These experts were asked to complete the matrix, indicating whether each listed conclusion was, to their knowledge, still valid, and if not, to provide information about new evidence (see Table 1 below).

Table 1. Sample questionnaire matrix

Conclusions From CER Executive Summary	Is This Conclusion Almost Certainly Still Supported by the Evidence?	Has There Been New Evidence That May Change This Conclusion?	Do Not Know
Key Question 1: What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?			
The prevalence of depression after traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27 percent of TBI patients met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 percent beyond 12 months. Higher prevalence is reported in many study populations. No strong predictors are available to select a screening window or to advise TBI patients or their providers about risk of depression.	☐	New Evidence:	☐
Key Question 2: When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?			
Prevalence of depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another. Likewise, the literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBIs. Nor does the literature support any one tool over the others.	☐	New Evidence:	☐

Table 1. Sample questionnaire matrix (continued)

Conclusions From CER Executive Summary	Is This Conclusion Almost Certainly Still Supported by the Evidence?	Has There Been New Evidence That May Change This Conclusion?	Do Not Know
Key Question 3: Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?			
When conditions were reported individually, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers. PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in no patients without depression, and panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression. Consideration of potential for coexisting psychiatric conditions is warranted.	☐	New Evidence:	☐
Key Question 4: What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and other therapies?			
Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain injury: Both were studies of antidepressant efficacy (one a controlled trial of sertraline and one an open-label trial of citalopram). The sertraline trial showed no significant effect compared with placebo, and the citalopram study did not show improvement in a majority of participants.	☐	New Evidence:	☐
Key Question 5: Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?			
No head-to-head trials were identified that compared the effectiveness of two or more modalities for treating depression that follows TBI. Such studies are needed.	☐	New Evidence:	☐

Table 1. Sample questionnaire matrix (continued)

Conclusions From CER Executive Summary	Is This Conclusion Almost Certainly Still Supported by the Evidence?	Has There Been New Evidence That May Change This Conclusion?	Do Not Know
Key Question 6: Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, preexisting mental health status or medical conditions, functional status, and social support?			
No studies were identified that assessed the impact of demographic or other potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Check for Qualitative and Quantitative Signals

Once abstraction of the study conditions and findings for each new included study was completed and expert opinions were received, we assessed whether the new findings provided a signal for the need to update, according to the Ottawa Method and/or the RAND Method, on a conclusion-by-conclusion basis. If new studies was deemed sufficiently similar to studies included in a pooled analysis in the original CER and were sufficiently large with respect to sample size, a new meta-analysis was conducted using the original pooled effect size as one data point in a random effects model. Table 2 lists the criteria used for reaching conclusions.[7,9]

Table 2. Ottawa and RAND Method

Ottawa's Label	Ottawa Method
	Qualitative Criteria for Potentially Invalidating Signals
A1	Opposing findings: A pivotal* trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Qualitative Criteria for Signals of Major Changes
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or non-pivotal trial
	Quantitative Criteria Signals of Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
RAND's Label	**RAND Method Indications for the Need for an Update**
1	Original conclusion is still valid and this portion of the original report does not need updating. This conclusion was reached 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.
2	Original conclusion is possibly out of date and this portion of the original report may need updating. This conclusion was reached 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.
3	Original conclusion is probably out of date and this portion of the original report may need updating. This conclusion was reached 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.
4	Original conclusion is out of date. This conclusion was reached 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.

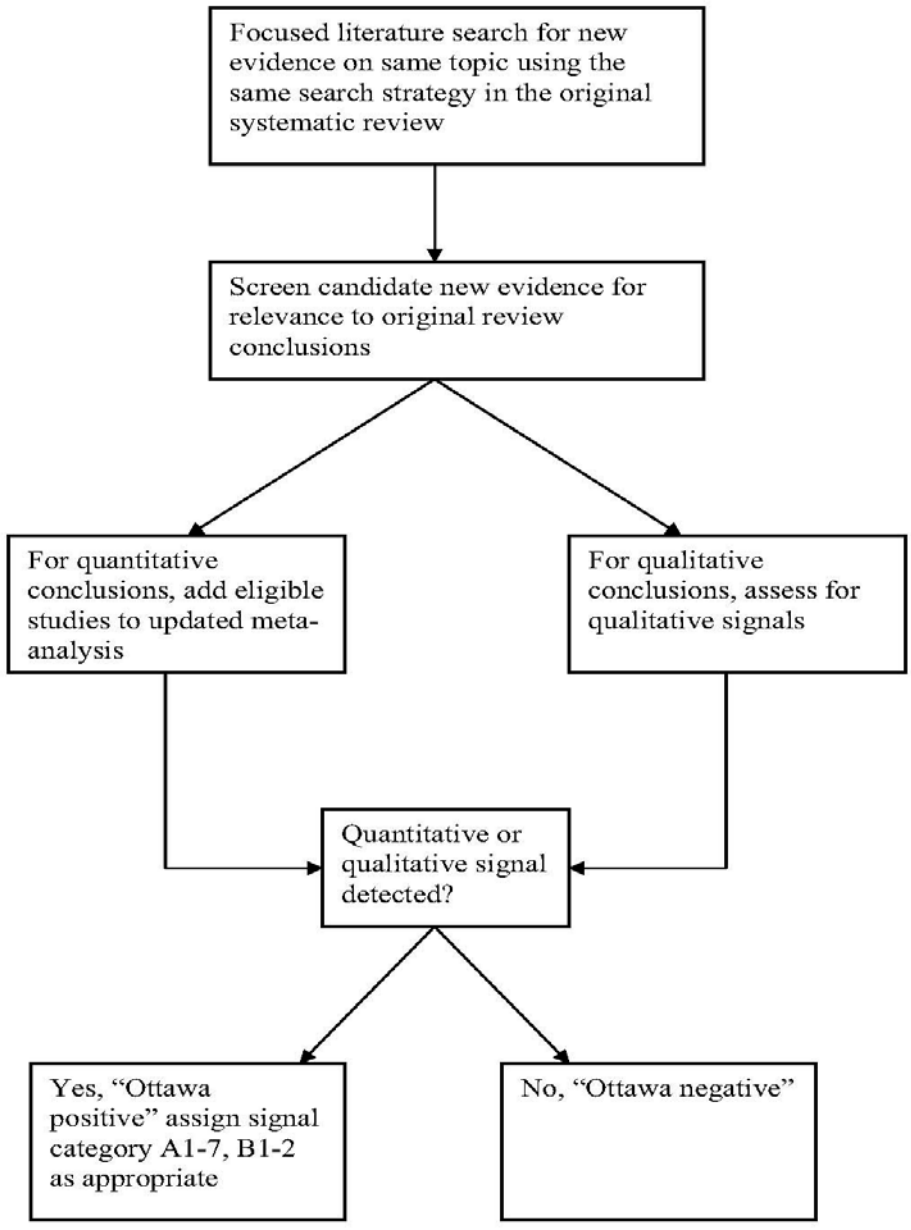
*A pivotal trial was defined as a trial published in one of the top 5 general medical journals (Annals of Intern Med, BMJ, JAMA, The Lancet, and NEJM), or a trial not published in the above top 5 journals but having a sample size at least triple the size of the largest trial in the original CER.

The Ottawa method involved detection of qualitative and/or quantitative signals indicating the need for updating through the assessment of new evidence using specific categories for

qualitative (A1–A7) and quantitative (B1–B2) signals, as reported in Table 2. For example, a finding from a newly published pivotal trial that was opposite to a corresponding conclusion in the original CER with respect to an efficacy outcome (e.g., effective vs. ineffective or vice- ersa) or harm (e.g., risk of harm outweighs the previously observed benefits), a superior new treatment (e.g., new treatment significantly more effective than one assessed in the CER), or a new population subgroup (the treatment assessed in the CER has been expanded to a new subgroup of participants) are each considered qualitative signals. An example of a quantitative signal is the incorporation of a new trial (or trials) into a meta-analysis conducted for the original CER that leads to a transformation of a previously statistically non-significant pooled estimate into a statistically significant one or vice-versa.

The specific steps involved in the Ottawa Method are shown in Figure 2.

Figure 2. Ottawa method



For each CER, we constructed a summary table that included the following for each Key Question: original conclusion(s), findings of the new literature search, summary of expert assessment, findings from the ECRI search of regulatory bodies, and our final assessment of the currency of the conclusion(s).

Determining Priority for Updating a CER

For each report, we provided an assessment as to whether each conclusion was up to date. We then needed to assign an overall judgment of the priority for updating. We used two criteria in making our final conclusion for a CER:

- 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 include the finding that some therapies are no longer favored or may no longer be in use? 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)?

This final conclusion was a global judgment made by all the individuals working on each particular CER. We classified CERs as being low, medium, or high priority for updating, with a notation explaining the rationale for high priority updates. If a therapy was no longer favored, no longer in use, or in question because of a safety concern, we would have recommended that, pending a full update, the original CER be withdrawn; however, no CERs presented this issue during our surveillance.

Summary Dissemination of Reports to AHRQ

We developed a format for a short summary report that presents the findings from the surveillance process to AHRQ. This format includes a title page that lists the final classification (low, medium, or high) of the priority for updating the CER; the details of the literature search and its yield (with evidence tables); the findings from FDA, Health Canada, and MHRA; the results of any expert opinion that was provided; and a summary table that contains each conclusion from the original CER and our assessment of the degree to which it may be out of date. Examples of such reports (one each judged as being at low, medium, and high priority for updating) are included in Appendix A.

Peer Review and Public Commentary

Experts were invited to provide external peer review of this report; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We received comments back from three reviewers and one public commentor. We have addressed all peer and public comments, revising the text as appropriate, and have documented all responses in a “disposition of comments report” that will be made available 3 months after the Agency posts the final report on the AHRQ Web site.

Results

Time To Complete the Surveillance Reports

Between June 2011 and June 2012 we evaluated 14 CERs. Table 3 indicates the CERs that were evaluated and the priority they received, the date of their release, and the date of when either the SCEPC or UOEPC sent the assessments to AHRQ. In addition, Table 3 presents the number of days to complete each of the 14 surveillance reports. The mean was 86 days and the median was 74 days, with the majority of reports being completed in 65 to 102 days.

The assessments of 14 CERs that were submitted by the SCEPC or UOEPC can be found on AHRQ's Web site (www.ahrq.gov) where the specific CER is located.

Table 3. Fourteen completed CER topics

CER	CER Topic	Release Date of Original CER	Completion Date for Most Recent Assessment	Days To Complete the Surveillance	Priority
13	Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer	2/1/08	5/18/12	74	High
15	Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation	7/6/09	11/30/11	69	Low
16	Comparative Effectiveness of Lipid-Modifying Agents	9/1/09	12/23/11	72	High
17	Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women	9/14/09	11/08/11	119	Medium
18	Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease	10/16/09	12/23/11	38	Low
19	Comparative Effectiveness of Core Needle Biopsy and Open Surgical Biopsy for Diagnosis of Breast Lesions	12/15/09	12/16/11	102	Medium
20	Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer	5/27/10	11/4/11	75	Medium
21	Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care	6/1/10	2/24/12	65	Low
22	Comparative Effectiveness of Nonoperative and Operative Treatments for Rotator Cuff Tears	6/5/10	2/24/12	65	Low
23	Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis	10/4/10	12/16/11	100	Low
25	Traumatic Brain Injury and Depression	4/13/11	4/10/12	161	Low
26	Comparative Effectiveness of Therapies for Children with Autism Spectrum Disorders	4/4/11	01/23/12	97	Low
30	Comparative Effectiveness of Pain Management Interventions for Hip Fracture	5/17/11	4/10/12	133	Low
35	Comparative Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth	9/29/2011	5/4/12	38	Low

Assessment Findings

The characteristics of the 14 CERs we assessed and the corresponding surveillance assessment results are presented in Table 4. Briefly, the number of Key Questions (KQs) across the 14 CERs ranged from three (CER No.s 16, 19) to seven (CER Nos. 23, 26). The median number of included studies in the CERs was 107 (range: 14–436). The number of newly identified studies deemed relevant for inclusion in the CERs ranged from 0 to 33, with a median of 15 studies.

Of the 14 CERs, 4 (29 percent) were up to date in the 12 to 59 months following their original search date (CER No.s 22, 23, 25, 35). For the remaining 10 CERs (CER Nos. 13, 15, 16, 17, 18, 19, 20, 21, 26, 30), at least one conclusion within a KQ changed in status from "up-to-date" to "probably/possibly out of date" or "out of date." In 4 of these 10 CERs (CER Nos. 13, 18, 19, 20), all conclusions within a KQ changed their status from "up-to-date" to "probably/possibly out of date" or "out of date."

Of the 14 CERs, 2 (14.3 percent) were assigned to high, 3 (21.4 percent) were assigned to medium, and 9 (64.4 percent) were assigned to low priority for updating. Of the 6 CERs released prior to 2010 (meaning more than 18 months prior to start of the Surveillance Program), 2 were judged as being high priority, 2 were judged as being medium priority, and 2 were judged as being low priority for updating. Of the remaining 8, only one was judged as being medium priority for updating. All but 1 of the CERs released within the year prior to the start of the Surveillance Program were judged as being low priority.

The percentage of experts asked who actually responded was also noted. The response rate ranged from 20 percent to 100 percent, with a median of 34.5 percent.

None of the 14 CERs for which we performed the surveillance assessments had an FDA black box warning associated with an agent, device, or procedure that was a topic of the CER (the strongest FDA warning, which indicates a significant risk of a serious or even life-threatening adverse effect). Five CERs had safety communications, adverse effects, and/or label change alerts (CER Nos. 16, 18, 23, 25, 26), none of which was sufficient to impact the updating priority of those CERs. CER No. 16 had a total of six label change alerts and three drug safety communication alerts, CER No. 18 had three alerts, and 3 CERs (Nos. 23, 25, 26) had one alert each.

Table 4. Characteristics of 14 comparative effectiveness reviews and their updating surveillance assessments

CER Title (AHRQ #) Author Name (Publication Date) [Journal Publication, if Available]	Latest Search Date for CER (Across Databases)	# of Included Studies in CER (Total or Per KQ)	Period Covered by Update Search	# Of New Studies Judged as Relevant for Inclusion in CER	Number of Conclusions Within the Key Questions in CER by Updating Status								Updating Priority for the CER		
					KQ#	# Conclusions Up To Date	KQ#	# Conclusions Probably Out of Date	KQ#	# Conclusions Possibly Out of Date	KQ#	# Conclusions Out of Date	Low	Medium	High
Assessed by RAND EPC															
Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer (13) Wilt (February 2008)[15] [Association Between Hospital and Surgeon Radical Prostatectomy Volume and Patient Outcomes: A Systematic Review][16]	September 2007	436	January 2007 to March 2012	21	1	11/15			1	2/15	1	2/15			x
											2	1/1			
					3	3/3									
					4	1/3					4	2/3			
Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women (17) Nelson (September 2009)[17] [Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer][18]	January 2009	13 (KQ1,KQ3) 70 (KQ2,KQ3) 24 (KQ4) 16 (KQ5)	January 2008 to July 2011	3	1	4/6	1	2/6						x	
					2	6/7	2	1/7							
					3	4/5	3	1/5							
					4- 5	9/9									
Comparative Effectiveness of Core Needle Biopsy and Open Surgical Biopsy for Diagnosis of Breast Lesions (19) Bruening (December, 2009)[19] [Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions][20]	September 2009	107 (KQ1-2) NA (KQ3)	January 2008 to September 2011	19	1	11/16			1a	4/16	1	1/16		x	
					2	3/4			2	1/4					
					3	1/2			3	1/2					

Table 4. Characteristics of 14 comparative effectiveness reviews and their updating surveillance assessments (continued)

CER Title (AHRQ #) Author Name (Publication Date) [Journal Publication, if Available]	Latest Search Date for CER (Across Databases)	# of Included Studies in CER (Total or Per KQ)	Period Covered by Update Search	# Of New Studies Judged as Relevant for Inclusion in CER	Number of Conclusions Within the Key Questions in CER by Updating Status								Updating Priority for the CER		
					KQ#	# Conclusions Up To Date	KQ#	# Conclusions Probably Out of Date	KQ#	# Conclusions Possibly Out of Date	KQ#	# Conclusions Out of Date	Low	Medium	High
Assessed by RAND EPC (continued)															
Effectiveness of Recombinant Human Growth Hormone (rhGH) in the Treatment of Patients With Cystic Fibrosis (23) Phung (October 2010)[21] [Recombinant human growth hormone in the treatment of patients with cystic fibrosis][22]	April 2010	26(KQ1-2, KQ4, KQ6-7) 50 (KQ3) 3(KQ5)	January 2010 to August 2011	16	1-7	40/40							x		
Comparative Effectiveness of Traumatic Brain Injury and Depression (25) Guillamondegui (April 2011)[23]	June 2010	115	January 2010 to October 2011	29	1-6	15/15							x		
Therapies for Children With Autism Spectrum Disorders (26) Warren (April 2011)[24] [A systematic review of early intensive intervention for autism spectrum disorders][25]	May 2010	159	January 2009 to October 2011	15	1	10/14			1	4/14			x		
					2	2/3			2	1/3					
					3-7	6/6									
Pain Management Interventions for Hip Fracture (30) Abou-Setta (May, 2011)[26] [Comparative effectiveness of pain management interventions for hip fracture: a systematic review][27]	December 2010	98	January 2008 to November 2011	1	1	7/8			1	1/8			x		
					2-4	39/39									

Table 4. Characteristics of 14 comparative effectiveness reviews and their updating surveillance assessments (continued)

CER Title (AHRQ #) Author Name (Publication Date) [Journal Publication, if Available]	Latest Search Date for CER (Across Databases)	# of Included Studies in CER (Total or Per KQ)	Period Covered by Update Search	# Of New Studies Judged as Relevant for Inclusion in CER	Number of Conclusions Within the Key Questions in CER by Updating Status								Updating Priority for the CER		
					KQ#	# Conclusions Up To Date	KQ#	# Conclusions Probably Out of Date	KQ#	# Conclusions Possibly Out of Date	KQ#	# Conclusions Out of Date	Low	Medium	High
Assessed by Ottawa EPC															
Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation (15) IP (July 2009)[28] [Systematic review: comparative effectiveness of radiofrequency catheter ablation for atrial fibrillation][29]	December 2008	120	June 2008 to September 2011	33	1	4/4							x		
					2	3/5			2	2/5					
					3	3/4			3	1/4					
					4	6/6									
Comparative Effectiveness of Lipid-Modifying Agents (16) Sharma (September 2009)[30] [Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dyslipidemia][31]	May 2009	101	November 2008 to October 2011	20	1	3/13					1	10/13			x
					2	34/48			2	14/48					
					3	9/25			3	16/25					
Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease(18) Coleman (October 2009)[32] [Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease][33]	February 2009	60	August 2008 to November 2011	12	1	6/7			1	1/7			x		
					2-6	28/28									
							7	4/4							

Table 4. Characteristics of 14 comparative effectiveness reviews and their updating surveillance assessments (continued)

CER Title (AHRQ #) Author Name (Publication Date) [Journal Publication, if Available]	Latest Search Date for CER (Across Databases)	# of Included Studies in CER (Total or Per KQ)	Period Covered by Update Search	# Of New Studies Judged as Relevant for Inclusion in CER	Number of Conclusions Within the Key Questions in CER by Updating Status								Updating Priority for the CER		
					KQ#	# Conclusions Up To Date	KQ#	# Conclusions Probably Out of Date	KQ#	# Conclusions Possibly Out of Date	KQ#	# Conclusions Out of Date	Low	Medium	High
Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care (21) Yank (May 2010)[34] [Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications][35]	August 2009	74	February 2009 to January 2012	15	2	2/3			2	1/3			x		
					3a	8/9			3a	1/9					
					3b	3/4			3b	1/4					
					4b-c	9/9			4a	1/2					
Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer (20) Samson (May 2010)[36]	September 2009	108	March 2009 to August 2011	7	1	2/3			1	1/3				x	
					2	1/2			2	1/2					
									3	1/1					
					4	3/3									
Comparative Effectiveness of Nonoperative and Operative Treatments for Rotator Cuff Tears (22) Sedia (July 2010)[37] [Systematic review: nonoperative and operative treatments for rotator cuff tears][38]	September 2009	137	March 2009 to January 2012	15	1-6	18/18							x		
Comparative Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth (35) Gaudet,(September 2011)[39] [Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth. A Systematic Review and Meta-Analysis][40]	April, 2011	14	October 2010 to March 2012	0	1-6	37/37							x		

KQ = Key Question; CER = comparative effectiveness review

Discussion

Ideally health care decisions and policy making should be informed and based on the most up-to-date scientific evidence.[41] Although the importance of updating systematic reviews has been well recognized internationally, there has been a relative paucity of research and initiatives towards maintaining the currency of systematic reviews.[2] An earlier, one-time assessment identified 4 out of 11 AHRQ published CERs as being sufficiently out of date that they should be updated or withdrawn.[7] These results indicated a need for the regular surveillance of AHRQ published CERs to assess their current validity. Therefore, the University of Ottawa EPC in collaboration with the Southern California EPC, assisted by ECRI, developed and piloted a system for surveillance and identification of signals for updating CERs published within the AHRQ Effective Health Care Program. This report describes the methodology and preliminary work behind the assessment of the need for updating for 14 AHRQ-funded CERs at least 6 months after their publication.

Our preliminary results indicate that a small proportion of CERs may be in need of urgent updating 1 to 3 years after their last search date. Of the 14 CERs assessed between June 2011 and June 2012, 9 (64 percent) were classified as having low priority for updating and 3 CERs (22 percent) had medium priority for updating. Two CERs (14 percent) were determined to have high priority for updating.

The implementation of the surveillance assessment program to determine the updating status of published AHRQ CERs has faced challenges. The assessment of currency and validity of conclusions for each KQ of a CER was based on the totality of information compiled through multiple sources including the qualitative/quantitative signals, expert opinion, and FDA, Health Canada, and MHRA alerts. Although we used operational and standardized definitions throughout the process to ensure relative consistency in the assessments, human judgment is required to interpret the newly identified evidence in relation to the conclusion of the CER. This judgment is a potential source of variability in the assessment. However, our prior work has shown that in at least one explicit assessment, the inter-rater reliability of these judgments was at least moderate.[14]

An additional challenge was the variability in presentation among the original CERs. Not all CER executive summaries presented the KQs and corresponding conclusions in an identical or even similar manner (e.g., degree of detail, format, or level of summarization). For example, in some CERs, conclusions for each KQ were stratified by the outcome and/or intervention, resulting in multiple conclusions. In other instances, executive summaries were not sufficiently detailed to be able to extract a specific, clearly formulated conclusion; therefore, the reviewers had to probe the entire body of text of the CER. Moreover, some conclusions were not readily amenable to assessing the need for updating with respect to comparative effectiveness. For example, some conclusions included descriptive information on prevalence of certain risk factors in specific populations.

In a few instances, experts differed in their opinions regarding whether or not a specific conclusion in a specific key question was potentially out of date, and the experts' opinions also differed from what the EPCs concluded was demonstrated in newly identified studies. Such differences may reflect differences in experts' knowledge of their respective content areas (AHRQ CERs enlist input from a diverse set of technical experts for exactly this reason), in how up to date they are in terms of the emerging literature,[42] or in interpretation of the clinical importance of new evidence. The surveillance program made a global judgment about how to weight expert opinion when it seemed to differ from the results of the literature search on a case-

by-case basis. Additionally, for most CERs, we received responses from fewer than 50 percent of the experts originally contacted; however, since the experts were not a random sample of all potential experts, the implications of this low response rate in terms of bias in the results are not as clear.

To our knowledge, this surveillance assessment project is the first effort of its scale that has applied methods to assess the updating status of evidence-based reports (or systematic reviews) in a structured and standardized manner. The application of these methods has proven to be relatively feasible, efficient, and at the same time a comprehensive and systematic approach for assessing the need for updating individual CERs across a wide range of health interventions. However, it is premature to generalize our findings to a broader population of CERs or systematic reviews, such as the finding that only a small proportion are high priority for updating within 1 to 3 years, and more data are needed on a larger number of CERs. Additionally, the predictive validity of the signals for updating deserve investigation. Such an investigation will be challenging, however, since it would need to assess both the false positive and the false negative outcomes of the signal, as well as adjusting for any new evidence that may accrue from the time the signals were detected until such time as a full update report could be completed. This latter task may often take 12 or more months.

Ideally the results of this surveillance assessment should be electronically linked to the original CER reports and any subsequent journal publications so that readers are advised regarding the CER's (or publication's) updating status and the Agency's assessment of when (and if) any given out-of-date CERs might be updated. We recognize that the decision to update a CER is a complex one, involving competing priorities, resources, and other emergent issues. As such, readers should not view all out-of-date CERs as reaching the same level of priority.

Given these preliminary results, we believe that this approach would potentially help AHRQ and other similar agencies in making informed decisions for prioritizing updating needs across different CERs (or systematic reviews). One of the main future objectives of this program should be to further harmonize and improve the above-described methods in terms of their feasibility, reproducibility, and applicability. The data collection and surveillance over time will allow us to gauge better what is the optimal time period or frequency needed for updating purposes. Among the first 14 CERs, only one released within one year prior to surveillance was classified as anything other than low priority for updating. If these preliminary results are confirmed, then a one year time frame for surveillance may be a more efficient interval for regular assessment.

Conclusions

We have established a surveillance program that evaluated 14 CERs over the course of 12 months. Regarding the need to update, 2 were classified as high priority, 3 as medium priority, and 9 as low priority, 12 to 59 months after the last search date of the original CER. We have shown that a program for regular and active surveillance of CERs is feasible.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CER(s)	Comparative Effectiveness Review(s)
EPC(s)	Evidence-based Practice Center(s)
FDA	U.S. Food and Drug Administration
MHRA	Medicines and Healthcare products Regulatory Agency

Appendix A. Examples of "Low," "Medium," and "High" Assessments

Appendix A-1: Example of a "Low" Priority Assessment
Appendix A-2: Example of a "Medium" Priority Assessment
Appendix A-2: Example of a "High" Priority Assessment

Appendix A contains examples of three CER Assessment reports, one for a CER deemed low priority for updating, one for a CER deemed medium priority, and one for a CER deemed high priority. The reports are shown in their entirety, including the appendixes that formed part of each report.

Appendix A-1. Example of a "Low" Priority Assessment

AHRQ Comparative Effectiveness Review Surveillance Program

CER #25 :
Traumatic Brain Injury and Depression

Original release date:
April 2011

Surveillance Report:
March 2012

Key Findings:
- All conclusions for KQ1-6 are still considered valid
- New significant safety concerns were identified including warnings about contraindications for one medication
- Several new studies were identified, including imaging studies aimed at linking neural changes to depression, a study assessing markers to predict treatment response, and several studies on non-pharmacological treatment modalities

Summary Decision
This CER's priority for updating is **Low**

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Contents

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Traumatic Brain Injury and Depression

1. Introduction

Comparative Effectiveness Review (CER) #25, Traumatic Brain Injury and Depression, was released in April 2011.[1] It was therefore due for a surveillance assessment in October, 2011.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Medline for the years 2010-October 20, 2011. Initially, this search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of Physical Medicine and Rehabilitation, Brain Injury, Journal of Head Trauma and Rehabilitation, and Journal of Neuropsychiatry and Clinical Neuroscience). The specialty journals were those most highly represented among the references for the original report. Because Medline does not index the *Journal of Neuropsychiatry and Clinical Neuroscience* and *Archives of Physical Medicine and Rehabilitation*, searches of these journals were performed using the Web of Science. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 16 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; four subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa

Method or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2,3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment 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 reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

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.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

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)?

3. Results

3.1 Search

The literature search identified 98 titles. After title and abstract review, we further reviewed the full text of 18 journal articles. The remaining 80 titles were rejected because they were editorials, letters, or did not include topics of interest. In addition to the searches, we also reference-mined articles that met inclusion criteria as well as non-systematic reviews identified by the literature searches but found no other articles. Eleven additional articles were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 29 articles went on to full text review. Of these, 15 articles were rejected because they were non-systematic reviews or did not include a comparison of interest. Thus, 14 articles were abstracted into an evidence table (Appendix B).[4-17]

3.2 Expert Opinion

The four experts were in agreement that none of the conclusions changed based on new evidence.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1: What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?				
The prevalence of [depression among individuals with] traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27 percent met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 percent beyond 12 months.	2 new studies confirmed prevalence findings from original report[5,16]	NR	4/4: No new evidence that would change conclusions; 1 of 4 experts recommended 2 new studies 1 expert suggested stratifying data by age, whether head injury closed or open, and nature of accident (e.g. car accident vs. fall)	Original conclusion is still valid and this portion of the original report does not need updating
Data are sparse to assess whether severity of injury influences risk of depression;	1 new study finds no association of injury (TBI) severity (GCS score or post-traumatic amnesia duration) with risk for depression[16]	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating
Stratification of prevalence by explanatory factors such as age, gender, area of brain injured, or mechanism of injury is not possible within the current body of literature	1 new study found no association between age, gender, time since injury and development of depression[8] 1 new study found that female gender, lower education, postinjury unemployment, and longer time since	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	injury were associated with a non-significant increase in the risk for depression, but length of education and current work status combined were a significant risk factor[4] 1 new study found that race and education had no association with depression; (younger) age, (female) sex, and cause of injury (intentional) were a major risk for depression; occupational status at time of injury showed a trend toward significance[16] 1 new study found that development of depression was associated with poorer progress in resuming preinjury lifestyle; timing suggests functional status contributes to depression[11] 1 new study using cross-lagged analysis suggests poor functional status at 6 months post TBI may predict development of depression at 12 months post TBI[9]			

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
History of alcohol and substance abuse increase risk. Pain, involvement in litigation related to the injury, and perceived stress have been reported as risk factors among those entering rehabilitation care and in prospective cohorts	1 new study identified preinjury depression as a significant risk factor for postinjury depression and confirmed a (non-significant) association with pain; [4] 1 new study found that preinjury substance abuse, and preinjury mental health tx, were all significantly related to depression ($p<0.005$)[16] 1 new study found the prevalence of axis 1 disorders (MDD, substance abuse) relatively high in the 12 months preceding a TBI, but significantly higher than the US population only for alcohol dependence[14]	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating
Imaging research about the areas of the brain injured and the relationship to depression risk yields inconsistent results. In aggregate for all those with TBI, onset of major depression within 3 months of injury has been reported to be sevenfold as common (95 percent CI: 1.36 to 43.48) among those	1 new study found no association between lesions in the frontal, temporal, or parietal lobes, sublobular lesions, or limbic lesions on MRI and depression. However, the ratio of right to left frontal lobe and parietal lobe volume ratios predicted depression with high accuracy. What is not clear is whether TBI	NR	No new evidence that would change conclusions but 1 expert cited [15], 1 cited research from literature on strokes as indicating an association between lesion location and depression risk, and 1 cited several military studies, including [12]	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
with abnormal CT scans after injury compared with normal imaging.	contributes to hemispheric imbalances in neural activity (unless it results from brain atrophy)[8] 1 new study found that the pathophysiology of post-TBI depression in terms of brain atrophy in 3 regions on MRI overlaps with that of spontaneous depression[15] 1 new study that used diffusion tensor imaging and functional MRI to examine structural and functional neural correlates of MDD in combat vets with TBI found that those with depression had greater activity during fear matching trials in the amygdala and other emotion procession areas and several other differences but the study could not prove that blast injury caused either the lesions or depression[12]			

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 2. When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?				
Prevalence of depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another.	No new information	NR	No new evidence that would change the conclusions	Original conclusion is still valid and this portion of the original report does not need updating
The literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBIs.	1 new study showed that no item of the PHQ-9 demonstrated statistically significant or meaningful differential item functioning attributable to TBI. Findings suggest PHQ-9 is a valid screener for MDD in people with TBI and that all items can be counted without concern regarding possible overdiagnosis.	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating
The literature does not support any one tool over the others.	No new information	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 3: Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?				
When conditions were reported individually, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers.	1 new study found that among individuals with TBI and depression, 23.5% had a substance use disorder and 73.5% had an anxiety disorder[5] 1 new study found that among individuals with TBI and depression, 13% and pre-existing anxiety disorder and 41% had a pre-existing substance use disorder [4] 1 new study reported that 3 to 6 months post TBI, 13% had both depressive and anxiety disorders and that at 6 to 12 months, 20% had both	NR	No new evidence that would change conclusions	Original conclusion is still valid and this portion of the original report does not need updating
PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in no patients without depression.	1 new study found that 10 of 11 patients with post-TBI MDD also had PTSD, compared with 9 of 11 TBI patients without MDD[12]	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating
Panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression.	1 new study found that 6 of 11 patients with post-TBI MDD also had panic disorder compared with 4 of 11 patients without MDD[12]	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Consideration of potential for coexisting psychiatric conditions is warranted.	No new research	NR	NR	Original conclusion is still valid and this portion of the original report does not need updating
Key Question 4. What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and other therapies?				
Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain injury: Both were studies of antidepressant efficacy (one a controlled trial of sertraline and one an open-label trial of citalopram). The sertraline trial showed no significant effect compared with placebo, and the citalopram study did not show improvement in a majority of participants.	1 new study found that a 12-week aerobics program improved HAM-D scores in individuals taking antidepressant medications such that the range of symptoms fell from moderate-severe and severe to mild-moderate and no symptoms. Scores on the Rosenberg Self-Esteem scale also improved, and the exercise had no adverse effects.[7] 1 new study found that a 6-week, internet-based cognitive behavioral therapy program decreased CES-D scores by a significant 1.03 points for each week completed. At 12 months followup, mean scores were 20.6±4.7 and PHQ-9 scores were 11.6±2.4,	MedWatch warning on taking sertraline with other agents that affect serotonin: Co-administration of Zoloft with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, fentanyl, 5-HT agonists, or the herbal medicine St. John's Wort (hypericum perforatum) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction. (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm) FDA MedWatch Precaution on lab tests: False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines. Health Canada: Citalopram - Association with abnormal heart rhythms (January 25, 2012) • A QT study showed that citalopram causes dose-dependent QT prolongation. • Citalopram should no longer be used in doses greater than 40mg/day • 20mg/d is the maximum recommended for patients with hepatic impairment, patients 65 years or older, patients who are CYP2C19 poor metabolizers, or patients who are taking cimetidine or another CYP2C19 inhibitor • Citalopram is contraindicated in patients with congenital long QT syndrome or known QT interval prolongation (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/celexa_2_hpc-cps-eng.php) Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety	No new evidence that would change conclusions but 1 expert cited [10]	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	significantly lower that at baseline. 4/16 completers had symptoms that declined to below MDD criteria.[6] 1 new study examined the effects of a double-blind placebo-controlled continuation of a 16-week open-label study of citalopram for TBI-associated depression in individuals who achieved remission. 1 participant dropped out due to side effects (diarrhea); all participants described at least 1 adverse event. Mean compliance was 91.9%. The relapse rate did not differ between treated and untreated participants (52%)[10]	Update: Antidepressants: Risk of Fractures (May 2010) Summary: Healthcare professionals should be aware of epidemiological data showing a small increased risk of fractures associated with the use of TCAs and SSRIs, and should take this risk into account in their discussions with patients and in prescribing decisions. Based on 9 observational studies in adults over 50. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085136		
Key Question 5. Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?				
No head-to-head trials were identified that compared the effectiveness of two or more modalities for treating depression that follows TBI. Such studies are needed	NR	NR	No evidence	Original conclusion is still valid and this portion of the original report does not need updating

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 6: Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, preexisting mental health status or medical conditions, functional status, and social support?				
No studies were identified that assessed the impact of demographic or other potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	In the citalopram blinded, placebo-controlled continuation study,[10] relapse was not predicted by age, sex, employment status or overall baseline or post-treatment HDRS scores. However 2 HDRS variables did predict higher risk for relapse: agitation and greater than mild psychic anxiety	NR	No new evidence that would change conclusions but 1 expert cited [13]	Original conclusion is still valid and this portion of the original report does not need updating
	In the original open-label citalopram study, certain small nuclear polymorphisms (SNPs) in genes associated with serotonin transport and metabolism predicted greater response to treatment and occurrence of adverse events.[13]			

Legend: PTSD= Post-Traumatic Stress Disorder; TBI=Traumatic Brain Injury; SNPs=Small Nuclear Polymorphisms; MRI=Magnetic Resonance Imaging; MDD= Major Depressive Disorder; NSSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2009-10/20/2011

LANGUAGE:
English

SEARCH STRATEGY:
Brain Concussion[mh] OR brain injuries[mh:noexp] OR Brain Hemorrhage, Traumatic[mh] OR Epilepsy, Post-Traumatic[mh] OR Head Injuries, Closed[mh] OR Head Injuries, Penetrating[mh] OR Intracranial Hemorrhage, Traumatic[mh] OR Craniocerebral Trauma[mh] OR TBI[tiab] OR head injuries[tiab] OR head injury[tiab] OR traumatic brain injury[tiab] OR traumatic brain injuries[tiab] OR neurotrauma[tiab] OR diffuse axonal injury[mh] OR diffuse axonal injury[tiab] OR brain trauma[tiab] OR head trauma[tiab]
AND
Depressive Disorder[mh] OR Depression[mh] OR depressive[tiab] OR depression[tiab] OR depressed[tiab] OR sadness[tiab] OR sad[tiab] OR hopelessness[tiab] OR suicidal[tiab] OR suicide[tiab] OR Mental Disorders[mh:noexp] OR mood[tiab]
AND
"Lancet Neurol"[Journal] OR "BMJ"[Journal] OR "BMJ (Int Ed)"[Journal] OR "JAMA"[Journal] OR "N Engl J Med"[Journal] OR "Ann Intern Med"[Journal] OR "Lancet"[Journal] OR **"Journal of head** trauma rehabilitation" OR J Head Trauma Rehabil OR american journal of psychiatry OR brain injury[journal]

NUMBER OF RESULTS: 76

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DATABASE SEARCHED & TIME PERIOD COVERED:
Web of Science - SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH – 2009-10/20/2011

LANGUAGE:
English

SEARCH STRATEGY:
Topic=(Brain Concussion* OR brain injuries OR brain injury OR Traumatic Brain Hemorrhage OR Post-Traumatic Epilepsy OR Head Injuries OR Intracranial Hemorrhage OR Craniocerebral Trauma OR TBI OR head injuries OR head injury OR traumatic brain injury OR traumatic brain injuries OR neurotrauma OR diffuse axonal injury OR diffuse axonal injury OR brain trauma OR head trauma)
AND

Topic=(depressive OR depression OR depressed OR sadness OR sad OR hopelessness OR suicid* OR Mental Disorders OR mood) AND Publication Name=(journal of neuropsychiatry and clinical neuroscience OR archives of physical medicine and rehabilitation)

NUMBER OF RESULTS: 22

Appendix B. Evidence Table

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
KQ1 What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?				
Author: Whelan-Goodinson, 2009 [5] Country, Setting: Monash University, Melbourne NSW; rehab hospital Enrollment Period: All admissions since inception Design: Observational study, cross-sectional, survey and medical record review Time from Injury: 0.5-5.5 years, mean of 3 yrs Length of Follow-up: NA Depression Scale/tool: SCID-I	Inclusion Criteria: Minimum age 17 years at the time of injury and maximum of 75 at time of interview; English proficiency, no history of previous TBI or serious neurological disorder e.g., stroke, epilepsy, brain tumor, or neurodegenerative disease; however patients with premorbid psychiatric Hx were not excluded. Exclusion Criteria: NR TBI Definition: NR	Group(s) N Screened: NR N eligible: NR N included: 100 N completed: 100 Depression: Prior to injury:17% At time of injury: unclear (20%? 3%? 17%?) Other pre-existing psychiatric conditions: Any anxiety disorder13%, Any psychiatric disorder: 1% Substance use disorder: 41% Eating disorder: 2% Age: 38±16.96 (19-67) Severity of TBI: Mean Glasgow coma Score at 1 year post injury 8.53±4.35 Mechanism/type of injury: NR Area of Brain injured: NR	Depression: NR but according to DSM-IV criteria Other co-morbidities: NR HRQOL or functional status: NR	46% of participants had depression at some time post injury, and 74% of those were depressed at the time of assessment. 8 people with current depression had a comorbid substance use disorder (23.5%) and 25 had a comorbid anxiety disorder (73.5%). 51.1% of those with depression were receiving medication and/or counseling, and 31.3% (5) of those whose depression had resolved were receiving counseling and/or medication.
Author: Whelan-Goodinson, 2010 [4] Country, Setting: Monash University, Melbourne	Inclusion Criteria: Glasgow Scale <15, considered cognitively capable of giving informed consent and being	Group(s) N Screened: NR N eligible: NR	Depression: NR but according to DSM-IV criteria	Predictors of postinjury disorders: The odds of developing depression were nearly 5 times

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
NSW; rehab hospital Enrollment Period: All admissions since inception Design: Observational study, cross-sectional, survey and medical record review Time from Injury: 0.5-5.5 years, mean of 3 yrs Length of Follow-up: NA Depression Scale/tool: SCID-I	reliable historians as deemed by the treating doctor or neuropsychologist, and sufficiently proficient in English to complete the interview Exclusion Criteria: Previous TBI or serious neurological disorder, e.g., stroke, epilepsy, brain tumor, or neurodegenerative disease TBI Definition: NR	N included: 100 N completed: 100 Depression: Prior to injury: 17% At time of injury: unclear (see[5] Other pre-existing psychiatric conditions: Any anxiety disorder13%, Any psychiatric disorder: 1% Substance use disorder: 41% Eating disorder: 2% Age: 38±16.96 (19-67) Severity of TBI: Mean Glasgow coma Score at 1 year post injury 8.53±4.35 Mechanism/type of injury: NR Area of Brain injured: NR	Other co-morbidities: NR HRQOL or functional status: NR Glasgow Outcome Scale Extended	higher in those with a history of preinjury depression; 13 of 17 cases with depression at some time in their lives prior to injury developed postinjury depression. Female gender, lower education, pain, postinjury unemployment, and longer time since injury were associated with greater likelihood of postinjury depression. In the logistic regression, history of preinjury depression was the only significant predictor of postinjury depression; however, longer time postinjury, pain, , and lower eduction approached significance in relation to postinjury depression. Current employment status and gender did not make significant individual contributions to this model. When length of education was combined with current work status (which are inter-related) were entered together, they made a significant contribution. Also, when history of preinjury depression was omitted, gender made a significant contribution (women were at higher risk for preinjury depression)
Author: Hart, 2011 [16] Country, Setting: US, multisite (academic, 19 nsites) participants in the Traumatic Brain Injury Model System [TBIMS] National Database Enrollment Period:	Inclusion Criteria: Receipt of medical care in a TBIMS-affiliated trauma center within 72 hours of injury, age >16, penetrating or non-penetrating TBI with at least 1 of the following characteristics: Glasgow Coma Scale score < 13 on emergency admission (not	Group(s) N Screened:2,274 N eligible: N included:1570 N completed:1570 (+ 350 who did not provide self-report depression data at follow-up)	Depression: Minor depression defined as 2-4 positive symptoms, major depression defined as ≥5 positive symptoms With at least 1 postivie cardinal symptom (depressed mood or anhedonia)	Prevalence: 52% of sample: reported no significant depression 22% reported minor depression 26% reported major depression Correlates: Race, education had no association with depression;

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Within 72 hours of injury, all enrollees from 10/06-06/09 Design: Before and after, at 1-year follow-up Time from Injury: 1 year Length of Follow-up: 1 year Depression Scale/tool: Patient Health Questionnaire (PHQ)-9 measures each of the 9 DSM-IV symptoms of major depression)	due to intubation, intoxication or sedation), loss of consciousness of more than 30 minutes (not due to sedation or intoxication), posttraumatic amnesia (PTA) more than 24 hours, or trauma related intracranial abnormality on neuroimaging Exclusion Criteria: Inability to complete PHQ-9, either due to inability to speak English or severe cognitive impairment TBI Definition: Score<13 on GCS, Duration of PTA (number of days between the TBI and the 1st of 2 occasions within 72 hours that the participant was fully oriented, i.e., a score>76 on the Galveston Orientation and Amnesia Test	Depression: Prior to injury: NR At time of injury: NR Other pre-existing psychiatric conditions: 43.2% positive for substance abuse pre-injury 19.6% positive for receipt of mental health treatment Age: 39.9±18.8 Severity of TBI: Mechanism/type of injury: 9.5% intentional cause of injury 62.1% vehicle-related 24.6% falls-related Area of Brain injured:	Other co-morbidities: NR HRQOL or functional status: FIM measured within 72 hours of injury and at 1-year	PTA duration and FIM at rehab discharge also were not associated with depression; GCS scores also were not associated with depression. (Younger) age, (female) sex, preinjury substance abuse, preinjury mental health tx, and cause of injury (intentional) were all significantly related to depression (p<0.005) Occupational status at time of injury showed a trend toward significance (p=0.006) [this paper also investigated the relationship of depression to 1-year outcomes such as cognitive and physical disability, global outcomes, and satisfaction with life, but these outcomes are beyond the scope of the review]
Author: Koponen 2011 [14] Country, Setting: Finland; academic medical center Enrollment Period: consecutive patients who visited emergency facility for TBI Design: Prospective observational study Time from Injury: < 3days Length of Follow-up: 12 months	Inclusion Criteria: (1) Acute brain trauma (< 3 days onset) that included one or more of the following: a. loss of consciousness for at least 1 minute (eye-witnessed by someone), b. post-traumatic amnesia (PTA) for at least 30 minutes; c. neurological signs or symptoms of brain injury during the first 3 days (excluding headache and nausea), or d. neuro-radiological findings indicating acute TBI; and (2) age between 16 and 70. Exclusion Criteria: Other CNS diseases	Group(s) 1 group only N Screened:45 N eligible:39 N included:39 N completed:38 (1 lost to FU) Depression: see findings Prior to injury: At time of injury: Other pre-existing psychiatric conditions: See findings Age: 41.6±17.0 (range 16-67) Severity of TBI:	Depression: NR Other co-morbidities: NR HRQOL or functional status: NR	During the 12 months preceding TBI, occurrence of axis 1 disorders was relatively high: alcohol abuse n=7 (18.4%); MDD n=4 (10.5%, 95% CI 2.9 to 24.8), Any Axis 1 disorder: n=15 (39.5%, 95% CI 24.0 to 56.6) When all disorders were taken into account (both pre-existing and new onset), 47.4% had any axis 1 disorder, and 6 had MDD (15.8%, 95% CI 6.0 to 31.3). Of those with onset after TBI, 5 had depressive disorders (13.2%, 95% CI 4.4 to 28.1). Of these 5, two developed depression NOS after TBI with no Hx of affective

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Depression Scale/tool: SCAN and SCID-II	TBI Definition: Glasgow coma scale at arrival combined with duration of PTA as follows: Mild TBI: GCS 13-15 and PTA< 24 hrs.; Moderate TBI: GCS 9-12 or PTA 1-7 days; Severe TBI: GCS≤8 or PTA>7 days; Very severe: PTA>4wks	27 (71.1%) mild, 6 (15.8%), moderate, 3 (7.9%) severe; 2 (5.3%) very severe Mechanism/type of injury: 26 (68.4%) falls; 10 (26.3%) 1 assault (2.6%), 1 other… Area of Brain injured: NR		disorders. One participant developed his first major depressive episode. Remaining two developed a major depressive episode after TBI(?). [so before TBI, alcoholism tended to be high, after TBI, depression tended to be high] Study also assessed axis II disorders. Rate was 29.0% (95% CI 15.4 to 45.9) Rate of Axis I disorders pre TBI was high but did not differ from that of the US community except for alcohol dependence (18.4%, 95% CI 7.7 to 34.3 vs. 3.9% and 1.3% in the community in Finland and the US, respectively).
Author: Ownsworth, 2011 [11] Country, Setting: NSW, major metropolitan hospital Enrollment Period: 9/07-7/09 Design: Prospective longitudinal observational study Time from Injury: Varied (hospital discharge and +3 months) Length of Follow-up: 3 months from hospital discharge Depression Scale/tool:	Inclusion Criteria: TBI from any cause, 18-60 years of age, hospitalized at least 4 days prior to discharge, adequate English skills Exclusion Criteria: NR TBI Definition: NR	Group(s) N Screened: 196 N eligible: N included: 129 N completed: 96 (22 w/d or loss to followup, 11 missing data) Depression: Prior to injury: At time of injury: Other pre-existing psychiatric conditions: Age: Mean age 35.37±13.07 (18-60) Severity of TBI:	Depression: DASS score ≥10 Other co-morbidities: NR HRQOL or functional status: Ability and Adjustment Index of the Mayo Portland Adaptability Inventory-4 (MPAI-4)	Proportion clinically depressed at discharge and 3 months later: 24%, 27% resp. At 3 months, 11.5% shifted from normal to clinically depressed and 11.55 had shifted from depressed to normal. Discharge DASS score was correlated with 3-month DASS score. Total transition events (Sentinel Events Questionnaire) correlated significantly with DASS-21 depression score at 3 months and with the MPAI-4 change score. Patients who progressed from normal to clinical depression had significantly poorer progress in

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Depression, Anxiety, and Stress Scales 21 (DASS-21)		Mean GCS (initial) 9.15±4.29 (3-15) Mechanism/type of injury: Traffic related (47.9%) Fa;; (27.1%) Assault (17.7%) Sporting injury (7.3%) Area of Brain injured: NR		resuming pre-injury lifestyle. Findings suggest the lack of progress in resuming normal lifestyle activities contributes to the postdischarge depressive symptoms through an influence on perceived function.
Author: Schönberger 2011 [9] Country, Setting: NSW Enrollment Period: Design: Time from Injury: Length of Follow-up: Depression Scale/tool: SCIDI	Inclusion Criteria: Complicated mild to severe TBI, age 16-80 at injury, no previous TBI or other neurological disorder, residence in Australia, sufficient cognitive and English ability to complete interviews Exclusion Criteria: TBI Definition:	Group(s) N Screened: 430 N eligible:276 N included: 172 N completed: (no differences between participants and those who declined except participants had more years of education) Depression: Prior to injury: NR At time of injury: NR 3-6 mos post injury: 19% had depressive disorder 6-12 mos post injury: 31% had a depressive disorder Other pre-existing psychiatric conditions: NR Age: 34.9±16.2 (median 28.3; range 16-77) Severity of TBI: 9.2±4.3 (median 9, range 3-15) Mechanism/type of injury:	Depression: NR Other co-morbidities: Anxiety: 3-6 mos: 13% of participants had both depression and anxiety 6-12 mos: 20% had both HRQOL or functional status: Extended Glasgow Outcome Scale (GOSE)	At 6 months post injury, 7% of participants had a severe disability in terms of functionality. 74% had moderate disability, 20% had good recovery. Cross-lagged analysis of depression and functional status showed that at 6 and 12 mos, poor functional status was not significantly related to the occurrence of depression. Poor functional status at 12 months was predicted by poor functional status at 6 months but not by depression at 6 months. *Occurrence of depression between 6 and 12 months post injury was predicted by depression at 6 months and by poor functional status at 6 months* ($p<0.048$), but depression (and anxiety) at 6 months did not predict later functional status, and the prediction of depression at 12 months from functional status at 6 months was not significantly stronger than the prediction of functional status at

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
		NR Area of Brain injured: NR		12 months from depression at 6 months.[seems somewhat contradictory; abstract emphasizes positive finding]
Author: Schönberger 2011 [8] Country, Setting: NSW Academic medical center Enrollment Period: NR Design: Cross-sectional Time from Injury: 2.2 yrs post-injury (0.3-5.7) Length of Follow-up: Not relevant Depression Scale/tool: SCID-IV	Inclusion Criteria: TBI with rehab at Epworth Hospital, absence of neurological conditions other than TBI, age 17-75, sufficient proficiency in English to complete structured psychiatric interview, suitability for MRI scanning, and no pre-injury hx of depression (via SCID-IV) Exclusion Criteria: NR TBI Definition: Glasgow Coma Scale	Group(s) N Screened:NR N eligible:NR N included:54 N completed:54 Depression: Prior to injury: none per inclusion criterion At time of injury: same Other pre-existing psychiatric conditions: NR Age: Mean 35.0, median 28.3, range 17-73, 61% 17-33 Severity of TBI: Mild to severe with most in the moderate-to severe range Mechanism/type of injury: NR Area of Brain injured: See results	Depression: Per SCID-IV Other co-morbidities: HRQOL or functional status: NR	13 (24%) developed a novel depressive disorder post-injury: 9 (69%) had a major depressive disorder and 4 (31%) had a DDNOS. 91% of participants had gray or white matter lesions on MRI. 80%: frontal lobe 65% temporal lobe 50% parietal lobe 67% sublobar 65% limbic No association was seen between DD and any of these lesions. Most participants had larger right frontal than left frontal lobes…DD was associated with a significantly more pronounced difference. (Cohen's d=0.9) Most participants also had larger right parietal than left parietal lobes: this difference was significantly smaller in individuals with DD. Both of these differences was independently associated with risk for DD. Age, gender, and time since injury did not predict DD. Frontal volume ratios predicted 31% of DD correctly, parietal volumes predicted 39%, and both predicted 46%. Non-depressed individuals were predicted with high accuracy using all three. However, it has

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
				not been definitively confirmed that TBI contributes to hemispheric imbalances in neural activity (unless the imbalance is the result of brain atrophy)
Author: Hudak 2011 [15] Country, Setting: US, Academic medical center Enrollment Period: 2005-2008 Design: Observational study on convenience sample Time from Injury: NR (mean time to 1st scan 3 days) Length of Follow-up: 6 months Depression Scale/tool: Beck Depression Index	Inclusion Criteria: 16-65 years of age, required admission to hospital for TBI Exclusion Criteria: 1) Preexisting neurological or psychiatric disorder or TBI; cognitive dysfunction; any condition that could result in an abnormal MRI; 2) presence of focal lesions; 3) contraindications to MRI; 4) prisoners, homeless, pregnant women TBI Definition:	Group(s) N Screened: N eligible: 72 N included: 58 N completed:25 (remaining participants eliminated because one scan missing) Depression: Prior to injury: No At time of injury: Other pre-existing psychiatric conditions: None Age: Median 23 (interquartile range [IQR] 19-37) Severity of TBI: Median 8 (IQR 3-14) Mechanism/type of injury: (64% motor vehicle collision, 9% motor cycle collision, 9% motor-pedestrian collision) Area of Brain injured: NR	Depression: Defined as BDI score >13 Other co-morbidities: NR HRQOL or functional status: Glasgow Outcome Scale-Extended: median 7 Functional status exam: Median 13	Structural imaging found some suggestive evidence that the pathophysiology of post-TBI depression overlaps with that of spontaneous depression. Atrophy (from 0 to 6 months post injury) in 3 regions of interest correlated significantly with depressive symptoms; these regions have been associated with spontaneous depression also.
KQ2. When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?				
Author: Cook, 2011 [17] Country, Setting: US, Level 1 trauma center and multisite primary care settings	Inclusion Criteria: TBI patients: admission to Harborview Medical Center, with TBI and radiologic evidence of acute, traumatically induced brain abnormality or	Group(s) N Screened: N eligible: N included:3000 primary care pts. and 365 TBI patients	Depression: PHQ-9 depression scale criteria Other co-morbidities: NR HRQOL or functional status: NR	The aim of this study was to assess whether any items of the PHQ-9 function differently in persons with TBI than in persons from a primary care sample in a way that would result in over-

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Enrollment Period: NR Design: Retrospective differential item functioning (DIF) analysis of data from 2 previous studies, one of primary care patients and one of TBI patients Time from Injury: Immediate up to 1 year Length of Follow-up: 1 year Depression Scale/tool: PHQ-9	GCS score<13 (lowest score within 24 hours after admission or 1st after withdrawal of paralytic agents), age≥18, English-speaking. Exclusion Criteria: TBI patients: uncomplicated mild TBI (GCS 13-15 and no radiologic abnormality), homelessness, no contact info, incarceration, and schizophrenia TBI Definition: GCS<13 or radiologic evidence	N completed: same Depression: Prior to injury: NR At time of injury: NR Other pre-existing psychiatric conditions: NR Age: TBI: 43±17.7 Primary Care: 46±17.2 Severity of TBI: NR Mechanism/type of injury: NR Area of Brain injured: NR		diagnosis of depression in TBI patients The results were that no PHQ-9 item demonstrated statistically significant or meaningful DIF attributable to TBI. Sensitivity analysis failed to show that the cumulative effects of non-significant DIF resulted in systematic inflation of PHQ-9 total scores. Thus the PHQ-9 is a valid screener of major depressive disorder in people with complicated mild to severe TB and that all symptoms can be counted toward a dx of major depressive disorder, without concern regarding over-diagnosis or unnecessary tx.
Author: Matthews, 2011 [12] Country, Setting: US, San Diego VAMC Outpatient Mood clinic Enrollment Period: NR Design: Cross-sectional multimodal neuroimaging study Time from Injury: 2.8 ±1 yr vs. 3.3±1.1 yrs for controls Length of Follow-up: NA	Inclusion Criteria: Experimental group: dx of major depression (MDD), prior blast exposure (blast injury) resulting in loss or alteration of consciousness at least 20 minutes Control group: no prior dx of MDD but had blast exposure Exclusion Criteria: Lifetime hx of ADHD, psychotic, bipolar, or chronic pain disorder; active medical problems, claustrophobia, suicidal ideation; alcohol/substance abuse or dependence within 30 days of the study	Group(s) N Screened:NR N eligible:NR N included: NR N completed: 11 per group Depression: Prior to injury: None At time of injury: none Other pre-existing psychiatric conditions: (excluded) Age: 26.8 (22-45) vs. controls: 30.3 (22-47)	Depression: Other co-morbidities: PTSD in 10/11 of MDD participants and 9/11 non-MDD participants Panic Disorder (6/11 and 4/11 resp.) HRQOL or functional status: NR	Aim of study was to use diffusion tensor imaging (DTI) and fMRI to examine the structural and functional neural correlates of MDD in Iraq combat vets with self-reported history of blast-related concussion. MDD participants showed greater activity during fear matching trials in the amygdala and other emotion processing areas, lower activity in emotion control areas (e.g., dorsolateral prefrontal cortex and lower fractional anisotropy (FA) in several white matter tracts, including the superior longitudinal fasciculus (SLF).

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Depression Scale/tool: Semi-structured interview based on DSM-IV, Beck Depression Inventory, PHQ-15	TBI Definition: DVBIC TBI screening tool - blast injury and loss or alteration of consciousness ≥20 minutes	Severity of TBI: NR Mechanism/type of injury: Blast injury Area of Brain injured: NR		Greater MDD symptom severity was negatively correlated with FA in the SLF. Results suggest biological basis for MDD in those with blast-related concussion. Study does not show that blast injury caused either the lesions or MDD
Author: Country, Setting: Enrollment Period: Design: Time from Injury: Length of Follow-up: Depression Scale/tool:	Inclusion Criteria: Exclusion Criteria: TBI Definition:	Group(s) N Screened: N eligible: N included: N completed: Depression: Prior to injury: At time of injury: Other pre-existing psychiatric conditions: Age: Severity of TBI: Mechanism/type of injury: Area of Brain injured:	Depression: Other co-morbidities: HRQOL or functional status:	
KQ3. Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?				
See articles under other KQ				
Key Questions 4-6 Treatment				
Author: Schwandt et al., 2010 [7]	Inclusion Criteria: 18-55 yrs >6 months since TBI	Group(s) Patients with TBI	Depression: Baseline HAMD scores (10-13: mild; 14-17: mild to moderate;	Depression: Baseline HAM-D scores 19-27 (all were taking medication)

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Country, Setting: Canada, Academic rehabilitation center (referrals from outpatient clinic) Enrollment Period: NR Design: Pre-post single group 12-week aerobic program with varying activities, depending on physical limitations. Training intensity was defined by rate of perceived exertion of 5-6 on Borg scale and heart rate 60-75% of age-predicted max. Training intensity maintained at 5-10W below baseline peak Time from Injury: >11 months (11 mos-7.2 yrs) Length of Follow-up: 12 weeks (end of program) Depression Scale/tool: HAM-D	Depression symptoms per MD report Able to communicate and follow instructions in English Exclusion Criteria: Substance abuse Psychiatric dx other than depression Suicidal ideation Medical conditions that would contraindicate participation Musculoskeletal or cognitive impairments TBI Definition: NR	N Screened:28 N eligible:16 N included:5 N completed:4 Depression: Prior to injury: At time of injury: Other pre-existing psychiatric conditions: Excluded Age: 19-48 yrs (mean 29) Severity of TBI: Mechanism/type of injury: Area of Brain injured: Varied with patient	18-25: moderate to severe; >25: severe): Other co-morbidities: NR HRQOL or functional status: NR	Post: decreases ranged from 9 to 16 Depression decreased from moderate to severe and severe to mild to moderate and no symptoms Fitness: Change in peak power output indicated improved aerobic fitness, Decreased heart rate in ¾ participants, Borg scores (5-10 →3-7) Rosenberg Self-Esteem Scale: (10-19 pre to 17-25 post) Frequency of attendance: 78% Ability to complete exercise: No adverse effects 9-question survey: indicated satisfaction with program; challenging but achievable.
Author: Topolovec-Vranic, 2010 [6] Country, Setting: Canada, Outpatient specialty clinic Enrollment Period: 12 mos. Design: Pre-post single group, 6-week internet-delivered CBT program Time from Injury:	Inclusion Criteria: Age ≥ 16 Dx of mild or moderate TBI (Glasgow Coma Score ≥ 9 following injury) English fluency Score ≥ 12 on PHQ-9 Regular access to internet, availability for weekly phone calls Originally, fewer than 5 years since TBI Exclusion Criteria:	Group(s) Single N Screened:391 N eligible:29 (excluded 88 refusers) N included:21 N completed:13 (16 completed at least 1 assessment; 9 completed 12-month follow-up) Depression: Prior to injury: (exclusion	Depression: Mean CES-D score at baseline for all 21 enrolled was 31.9±1.7 Mean PHQ-9 score at baseline for all enrolled was 17.4±0.9 Mean CES-D score for completers was 30.7±2.3 Other co-morbidities: NR HRQOL or functional status: NR	CES-D scores decreased by 1.03 pts for each week of the intervention completed ($p<0.0001$). At the 12-month followup, mean CES-D score in the 9 participants assessed was 20.6±4.7 At the 12-month followup, mean PHQ-9 score was 11.6±2.4, significantly lower than at baseline ($p<0.05$), and 4 of the completers had scores<12,

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
Mean 2.1 years, (0.1-7.3) Length of Follow-up: 12 months Depression Scale/tool: CES-D, PHQ-9	Pre-existing psychopathology (prior to injury), refusal to participate TBI Definition: Based on Glasgow Coma Score	criterion) At time of injury: (exclusion criterion) Other pre-existing psychiatric conditions: (exclusion criterion) Age: Mean 42.5 (19.3-72.3) Severity of TBI: GCS 13-15: 43% GCS <13: 29% NA: 29% Mechanism/type of injury: NR Area of Brain injured: NR		indicating symptoms had declined to <major depression criteria. Completion rates were not predicted by any demographic or injury variables assessed. Main challenge reported by those using the site was that it was difficult to read, remember, and sometimes understand
Author: Rapoport, 2010 [10] Country, Setting: Canada, academic TBI clinic Same population as Lanctot et al., 2010 (and Rapoport 2008?). Enrollment Period: Weks 10-16 of active, open-label treatment Design: Randomized double-blind, placebo-controlled trial following open-label trial. Ten participants were randomly assigned to continue the dose of citalopram they were taking at the end of the open-label trial, and 11 were assigned to taper off over 2 weeks and continue on placebo. Capsules were blinded	Inclusion Criteria: Participation in open-label citalopram study and achievement of remission Exclusion Criteria: NR (See Lanctot) TBI Definition: According to Lanctot, mild TBI was defined as loss of consciousness at time of injury of 20 minutes or less, an initial GCS score of 13–15, and post-traumatic amnesia (PTA) of less than 24 hours. Moderate to severe TBI had a GCS score of less than 13, a PTA greater than 24 hours, or an abnormal CT image	Group(s) N Screened: NR N eligible: NR N included: 21 N completed: 18 Depression: Prior to injury: Excluded At time of injury: Other pre-existing psychiatric conditions: Excluded Age: Mean = 47.67±19.9, range 21-85 Severity of TBI:	Depression: Other co-morbidities: HRQOL or functional status:	18 of 21 participants completed the study. (reasons for dropping out were side effects [1 participant, diarrhea] or desire to stop taking medication) Mean compliance at the first postrandomization visit (via pill counts) was 91.9% for 16 participants (76.2%). 14 of 16 participants had a compliance of 85% or more. AT the final visit, pill counts were available for 18 participants (85.7%) and showed a mean compliance of 94.8%, with all having a compliance of 85% or greater. At baseline, groups differed only in education level and MMSE score (citalopram group had a

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
via overencapsulation. Time from Injury: 3.3±3.2 mos plus 10-16 weeks; only 1/3 of patients assigned at 10 weeks Length of Follow-up: 40 weeks or until relapse Depression Scale/tool: Hamilton Depression Rating Scale		Mild in 16 participants (76.2%) and moderate in 4 (19.0%); 1 participant had a GCS rating<9 due to hemorrhage from a mesenteric tear and sedation but he was recovering. Mechanism/type of injury: NR Area of Brain injured: NR		slightly higher score 28.8±1.0 vs. 25.9±3.9, p=0.036) Relapse was seen in 11 of 21 (52.4%) of participants. Relapse rates did not differ between groups. All participants described at least one AE. Subgroup analysis to try to identify predictors of relapse found no effect of age, sex, employment status or overall baseline or post-treatment HDRS scores. 2 HDRS variables did predict higher risk for relapse: more than mild psychic anxiety and agitation. Thus drug treatment did not decrease risk for relapse…
Author: Lanctot 2010 [13] Country, Setting: Canada, academic TBI clinic Enrollment Period: Patients recruited from larger cohort of consecutive referrals from 2003-2007 Design: Open-label study of citalopram (20mg/d) Time from Injury: 3.3±3.2 mos Length of Follow-up: 6 wks Depression Scale/tool:	Inclusion Criteria: Mild to moderate TBI and dx of major depressive episode. Exclusion Criteria: Individuals with prior focal brain disease (e.g., stroke, tumor), significant acute medical illness, alcohol abuse, CT abnormalities inconsistent with TBI, current antidepressant tx, contraindications to citalopram, or premorbid dx of schizophrenia, BPD, or dementia TBI Definition: Mild TBI was defined as loss of consciousness at time of injury of 20 minutes or less, an initial	Group(s) N Screened: NR N eligible: 560 N included:NR N completed:90 Depression: Prior to injury: Excl? At time of injury: Other pre-existing psychiatric conditions: Excluded Age: 39.9±18.0	Depression: Depression module of the SCID Axis I disorders Other co-morbidities: 46.7% had focal injuries, 2.2% had atrophy on CT scan HRQOL or functional status: NR	Aim of the study was to assess whether certain small nuclear polymorphisms (SNPs) in 65HTTLPR (serotonin transporter), 5HT1A C…, 5HT2 T-…, MTHFR, brain-derived neurotropic factor (BDNF), val66met, and tryptophan hydroxylase-2(TPH2)… genes associated with serotonin metabolism affected response to treatment (efficacy and adverse events). MTHFR and BDNF SNPs predicted greater tx response (R^2=0.098, p=0.013), and the 5HTTLPR predicted greater occurrence of AEs (R2=0.069, p=0.020). Thus SNPs

Study Description	Inclusion/Exclusion Criteria	Population and Baseline Characteristics	Study Definitions	Findings (Depression Incidence/Prevalence, Comorbidities, Risk Factors, Effx of Tx)
HAM-D and Depression module of the SCID Axis I disorders	GCS score of 13–15, and post-traumatic amnesia (PTA) of less than 24 hours. Moderate to severe TBI had a GCS score of less than 13, a PTA greater than 24 hours, or an abnormal CT image	Severity of TBI: Majority met criteria for mild to moderate TBI Mechanism/type of injury: Area of Brain injured:		might help predict short term response to and tolerability of citalopram in patients with MDE following TBI.
Of minor relevance to KQ5 (not specific to individuals with depression following TBI): FDA (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm271273.htm) MedWatch warning on taking sertraline with other agents that affect serotonin: Co-administration of Zoloft with other drugs which enhance the effects of serotonergic neurotransmission, such as tryptophan, fenfluramine, fentanyl, 5-HT agonists, or the herbal medicine St. John's Wort (hypericum perforatum) should be undertaken with caution and avoided whenever possible due to the potential for pharmacodynamic interaction. FDA MedWatch Precaution on lab tests: False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking sertraline. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of sertraline therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.				

Legend: TBI=Traumatic Brain Injury; TBIMS= Traumatic Brain Injury Model System; PTA= Posttraumatic Amnesia; DASS21= Depression, Anxiety, and Stress Scales 21; IQR= Interquartile Range; SNPs=Small Nuclear Polymorphisms; TPH2=Tryptophan Hydroxylase-2; DTI=Diffusion Tensor Imaging; SLF=Superior Longitudinal Fasciculus; DIF=Differential Item Functioning; DDNOS=Dissociative Disorder Not Otherwise Specified; FA=Fractional Anisotropy; GOSE=Extended Glasgow Outcome Scale; MRI=Magnetic Resonance Imaging

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Traumatic Brain Injury and Depression

The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: What is the prevalence of depression after traumatic brain injury, and does the area of the brain injured, the severity of the injury, the mechanism or context of injury, or time to recognition of the traumatic brain injury or other patient factors influence the probability of developing clinical depression?			
The prevalence of depression after traumatic brain injury is approximately 30 percent across multiple time points up to and beyond a year. Based on structured clinical interviews, on average 27 percent of TBI patients met criteria for depression 3 to 6 months from injury; 32 percent at 6 to 12 months; and 33 percent beyond 12 months. Higher prevalence is reported in many study populations. No strong predictors are available to select a screening window or to advise TBI patients or their providers about risk of depression.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 2: When should patients who suffer traumatic brain injury be screened for depression, with what tools, and in what setting?			
Prevalence of depression is high at multiple time points after TBI. No evidence provides a basis for targeting screening to one timeframe over another. Likewise, the literature is insufficient to determine whether tools for detecting depression that have been validated in other populations can accurately identify depression in individuals with TBIs. Nor does the literature support any one tool over the others.	☐	New Evidence:	☐
Key Question 3: Among individuals with TBI and depression, what is the prevalence of concomitant psychiatric/behavioral conditions, including anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse, and major psychiatric disorders?			
When conditions were reported individually, anxiety disorder was most prevalent and affected from 31 to 61 percent of study participants in four papers. PTSD, a major anxiety disorder, was observed in 37 percent of depressed patients and in no patients without depression, and panic disorder was seen in 15 percent of patients with major depression, but not measured in those without depression. Consideration of potential for coexisting psychiatric conditions is warranted.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 4: What are the outcomes (short and long term, including harm) of treatment for depression among traumatic brain injury patients utilizing psychotropic medications, individual/group psychotherapy, neuropsychological rehabilitation, community-based rehabilitation, complementary and alternative medicine, neuromodulation therapies, and other therapies?			
Only two publications addressed treatment for individuals diagnosed with depression after a traumatic brain injury: Both were studies of antidepressant efficacy (one a controlled trial of sertraline and one an open-label trial of citalopram). The sertraline trial showed no significant effect compared with placebo, and the citalopram study did not show improvement in a majority of participants.	☐	New Evidence:	☐
Key Question 5: Where head-to-head comparisons are available, which treatment modalities are equivalent or superior with respect to benefits, short- and long-term risks, quality of life, or costs of care?			
No head-to-head trials were identified that compared the effectiveness of two or more modalities for treating depression that follows TBI. Such studies are needed.	☐	New Evidence:	☐
Key Question 6: Are the short- and long-term outcomes of treatment for depression after TBI modified by individual characteristics, such as age, preexisting mental health status or medical conditions, functional status, and social support?			
No studies were identified that assessed the impact of demographic or other potentially modifying characteristics on treatment effectiveness. Future research needs to address this issue.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Appendix A-2: Example of a "Medium" Priority Assessment

AHRQ Comparative Effectiveness Review Surveillance Program

CER # 20:

Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer

Original release date:

May 27, 2010

Surveillance Report:

October, 2011

Key Findings:

- 1 of 3 conclusions for KQ1 possibly out of date
- 1 of 2 conclusions for KQ2 possibly out of date
- 1 of 1 conclusions for KQ3 possibly out of date
- KQ4 up to date
- Expert opinion: conclusions for KQ1-4 still valid
- There are no new significant safety concerns

Summary Decision:

This CER's priority for updating is **Medium**

Authors:

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Technical support: Raymond Daniel

Advisory panel: David Moher, Mohammed Ansari

Oversight/supervision: David Moher, Chantelle Garritty

None of the investigators has any affiliation or financial involvement that conflicts with material presented in this report

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1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 20 (Comparative effectiveness and safety of radiotherapy treatments for head and neck cancer), is in need of updating.[1] This CER was originally released in May, 2010. It was therefore due for a surveillance assessment in November, 2010. When the Surveillance program began in the summer of 2011, this CER was selected to be in the first wave of reports to go through the assessment.

This CER included 108 unique studies identified by using searches through the September 28, 2009 and addressed four key questions to compare alternative radiotherapy modalities in the treatment of head and neck cancer. The following four treatment modalities were compared: intensity-modulated radiotherapy (IMRT), 3-dimentional conformal radiotherapy (3DCRT), 2-dimentional radiotherapy (2DRT), and proton beam. The key questions of the original CER were as follows:

1. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?
2. What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?
3. Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?
4. Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?

The conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, FDA surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.[2-4]

2.1 Literature Searches

The original CER search strategies were reconstructed in MEDLINE (March 29, 2009-August 22, 2011), EMBASE (2009 to 2011 Week 33), and Cochrane Central Register of Controlled Trials (CCRCT; search date: August 22, 2011). The original CER search strategies for update search purposes were derived from the PubMed strategy appearing in the Appendix A.[1] The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were adjusted according to the three databases indicated in the appendix and in the search strategy section of the report. Journal titles were entered according to the style used by each of the selected OVID databases. The electronic searches in MEDLINE and EMBASE were limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (Journal of Surgical Oncology, Cancer Radiotherapy, Breast Cancer Research, British Journal of Cancer, Cancer, International Journal of Radiation Oncology Biology Physics, Journal of Clinical Oncology, Radiotherapy & Oncology, Head & Neck). Restricting by journal title was not possible in the Cochrane search and pertinent citations were instead selected from the results. Study design filters were not applied to any of the searches although the Cochrane Central Register only contains randomized or controlled clinical trials. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as one described in the original CER.

2.3 Expert Opinion

In total, 3CER-specific (e.g., lead author, clinical content experts, and technical expert panel members) and 8 additional (local) clinical content experts were requested to provide their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B.

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and FDA surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and FDA surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

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 up to date.
- 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.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?

- How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 483 bibliographic records were identified (MEDLINE=199, EMBASE=260, and CCRCT =24). After de-duping, 308 records remained (MEDLINE=183, EMBASE=124, and CCRCT=1), from which 15 potentially eligible records were assessed for full text. Of these, seven were included in the update.[5-11]

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study, population, treatment characteristics, and results for the seven included studies[5-11] are presented in Appendix C (Evidence Table). In brief, one study was a pivotal randomized controlled trial[7] and the remaining six were non-pivotal observational cohort studies.[5,6,8-11] The randomized trial included 94 participants. The sample size of the cohort studies ranged from 51[8] to 1276. [5] The included studies compared intensity-modulated radiotherapy (IMRT) to two-dimensional radiotherapy (2DRT) alone, [5,8,9] three-dimensional conformal radiotherapy (3DCRT) alone,[7,10,11] or both treatments (3DCRT or 2DRT)[6] in relation to overall (or disease-free) survival,[5,7-11] incidence of late xerostomia[7,8,10,11] incidence of other adverse events (e.g., acute xerostomia, mucositis, acute dysphagia, skin/bone toxicity, late osteoradionecrosis), [8,10,11] quality of life (QOL),[6,7] and tumor control (local/distant).[5,8-11]

3.2.2 Qualitative signals

Key question #1

Late Xerostomia: all studies, including one pivotal trial that reported the incidence of late xerostomia showed significantly reduced rates of late xerostomia for IMRT compared to either 3DCRT[7,10,11] or 2DRT.[8] Given the similar findings/conclusions with respect to late xerostomia in the original CER, we did not identify any signal for this outcome that would trigger an update. **No signal**

Other Adverse Events: The incidence of other adverse events (i.e., mucositis, acute xerostomia, dermatitis) in two studies was significantly reduced for IMRT treatment groups compared to 3DCRT groups.[10,11] However, in one study,[8] the rate of mucositis was significantly higher in the IMRT vs. 2DRT treatment group (28% vs. 12%, p=0.01). This finding is in accord with that from the original CER which also reported inconsistent results for other adverse events. **No signal**

Quality of life: The pivotal trial and one cohort study showed no significant difference in QOL between IMRT and 3DCRT.[6,7] The same cohort study showed a significantly improved QOL for the IMRT group compared to the 2DRT. The finding of no difference in QOL between IMRT and 3DCRT is in conflict with that reported by the original CER, which indicated significant superiority of IMRT over 3DCRT in improving QOL. **One signal (A1)**[1]

Key question #2:

Survival: The pivotal trial[7] and five cohort studies[5,8-11] showed no significant differences in the 2-5-year overall survival between patients receiving IMRT and 3DCRT (or 2DRT). Note that these non-significant results are inconclusive due to very small sample sizes of five studies [7-11] and the

[1] see Appendix B and Shojania et al. 2007[2] for the definitions/classification of signals

lack of reported 95% confidence intervals for four of them.[8-11] Similarly, the evidence from the original CER regarding the difference in the overall survival rate between IMRT vs. 3DCRT (or 2DRT) was insufficient and inconclusive. **No signal**
Tumor control: In four cohort studies,[8-11] 2-3 year tumor control (local/distant) was not significantly different after receiving IMRT compared to 3DCRT (or 2DRT). These non-significant differences were inconclusive due to very small sample sizes and the lack of reported 95% confidence intervals. Likewise, the evidence from the original CER regarding the difference in tumor control between IMRT vs. 3DCRT (or 2DRT) was insufficient and inconclusive. However, there was a large cohort study with a longer follow-up[5] which, showed a significantly improved 5-year local tumor control in favor of IMRT vs. 2DRT (92.7% vs. 86.8%, p=0.007). **One signal (A7)**

Key question #3:
Survival: One large cohort study with a longer follow-up [5] indicated significantly improved 5-year survival for IMRT vs. 2DRT in T1 stage patients (100% vs. 94.4%, p=0.016), as opposed to no significant difference in survival for all patients (75.9% vs. 71.4%, p=0.088). No studies answering this key question were identified in the original CER. **One signal (A7)**

Key question #4:
None of the included 7 studies provided any evidence to answer this key question. Similarly, no such studies were identified and included in the original CER. **No signal**

3.2.3 Quantitative signals
Since the CER did not include a meta-analysis, only the presence/absence of qualitative signals was examined.

3.3 FDA surveillance alerts
None of the received FDA surveillance alerts was relevant to radiotherapy treatments for head and neck cancer.

3.4 Expert opinion
Three (one CER-specific and two local) of the 11 contacted clinical experts provided their responses/feedback in the matrix table (Appendix D). The responses from all three experts were consistent in agreement that all four conclusions (outlined in the executive summary of the original CER) were still valid and the experts were not aware of any new evidence that would invalidate these conclusions. One expert noted that one pivotal randomized trial previously included in the original CER as an abstract, has now been published as full text report. [7]

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from newly identified studies, FDA surveillance alerts, and expert opinion) are provided in Table 1 (summary table). Based on the assessments (see below), this CER is categorized in **Medium** priority group for updating.

Key Question # 1
Signals from update search: One pivotal trial and one cohort study showed no significant difference in QOL between IMRT and 3DCRT. The original CER indicated significantly better QOL in IMRT vs. 3DCRT. **One signal (A1).**
Experts: All stated the conclusions for key question #1 are still valid.
FDA surveillance alerts: No relevant safety alerts.
Conclusion: **1 of 3 conclusions for Key Question # 1 is possibly out of date.**

Key Question # 2
Signals from update search: One large longer-term follow-up (5 years) cohort study showed that IMRT group of patients had an improved tumor control compared to 2DRT group of patients. The original CER indicated the lack of evidence for this comparison. **One signal (A7).**
Experts: All stated the conclusions for key question #2 are still valid.
FDA surveillance alerts: No relevant safety alerts.
Conclusion: **1 of 2 conclusions for Key Question # 2 is possibly out of date**.

Key Question # 3
Signals from update search: One large longer-term follow-up (5 years) cohort study showed significantly improved survival for IMRT compared to 2DRT for T1 stage patients. The original CER indicated the lack of evidence for this Key Question. **One signal (A7).**
Experts: All stated the conclusions for key question #3 are still valid.
FDA surveillance alerts: No relevant safety alerts.
Conclusion: **The only conclusion for Key Question # 3 is possibly out of date.**

Key Question # 4
Signals from update search: No new study identified. The original CER indicated the lack of evidence for this Key Question. **No signal.**
Experts: All stated the conclusions for key question #4 are still valid.
FDA surveillance alerts: No relevant safety alerts.
Conclusion: **Up to date.**

Table 1. Summary Table

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA surveillance alerts	Expert opinion (CER + local)	Conclusion on validity of CER conclusion(s)
		Qualitative	Quantitative			
Key Question 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?						
The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points.	1 RCT[7] and 4 cohort studies [6,8,10,11]	**No signal** Findings in studies identified from update search were in agreement with those from the original CER in indicating reduced late xerostomia rates in IMRT vs. 3DCRT or 2DRT	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question #1) is still valid; one expert noted the publication of full text of an RCT[7] – pivotal trial	Up to date
The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent.	3 cohort studies [8,10,11]	**No signal** 2 studies showed significantly reduced rates of adverse events in IMRT compared to 3DCRT, but in another study the rate of mucositis was higher in IMRT compared to 2DRT. Similarly inconsistent results for adverse events were found in the original CER				Up to date
Quality of life was reported in three observational	2 cohort studies	**1 signal (A1)**				Possibly out of date

studies and generally favored IMRT in domains primarily related to xerostomia, such as dry mouth, swallowing, and sticky saliva	[6,7]	The pivotal trial and one cohort study showed no significant difference in QOL between IMRT and 3DCRT. This is opposing to the finding of the original CER, where IMRT was better than 3DCRT in improving QOL				
Key question 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?						
No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias	1 RCT[7] and 5 cohort studies [5,8-11]	**No signal** The evidence from update search and the original CER showed no significant differences in the 2-5-year overall survival between IMRT and 3DCRT (or 2DRT) and was inconclusive due to very small sample sizes and/or failure to report 95% CIs **1 signal (A7)** Although results of studies from update search and those in the original CER were consistent in showing no	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question #2) is still valid	Up to date Possibly out of date

		significant difference in 2-3 year tumor control between IMRT and 3DCRT, one large cohort study with a longer follow-up reported that IMRT compared to 2DRT improved 5-year local tumor control				
Key question 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?						
No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	1 cohort study [5]	**1 signal (A7)** The original CER did not include studies answering this key question. One large cohort study from the update search showed significantly improved 5-year survival for IMRT vs. 2DRT in T1 stage patients	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question #3) is still valid	Possibly out of date
Key question 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?						
No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	No included studies	NA	NA (no meta-analysis in CER)	None	All 3 experts stated that this conclusion (for key question # 4) is still valid	Up to date
CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy; FDA=food and drug administration; NA=not applicable; QOL=quality of life; CI=confidence interval						

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Appendix A: Search Methodology

All MEDLINE and EMBASE searches were limited to the following journals:

General biomedical - Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine

Specialty journals - Journal of Surgical Oncology; Cancer Radiotherapy; Breast Cancer Research; British Journal of Cancer; Cancer; International Journal of Radiation Oncology Biology Physics; Journal of Clinical Oncology; Radiotherapy & Oncology; Head & Neck.

Database: Ovid MEDLINE(R)

Time period covered by the search: March 29, 2009 to August 22, 2011

1 exp "Head and Neck Neoplasms"/ (215693)

2 (larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or oral or paranasal or para-nasal or nasal or sinus or salivary or parotid).ti,ab. (642746)

3 (neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or adenocarcinoma or carcinoma).ti,ab. (1727955)

4 ("occult primary" or "unknown primary").ti,ab. (2392)

5 2 and (3 or 4) (105790)

6 1 or 5 (262889)

7 exp Radiotherapy, Conformal/ (7307)

8 (IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT").ti,ab. (3992)

9 (intensity and modulated).ti,ab. (6276)

10 (conformal or proton or protons).ti,ab. (72737)

11 protons/ (22260)

12 or/7-11 (88262)

13 6 and 12 (2378)

14 limit 13 to human (2282)

15 (in process or publisher or pubmednotmedline).st. (182775)

16 13 and 15 (26)

17 14 or 16 (2308)

18 jama.jn. (61187)

19 "annals of internal medicine".jn. (26637)

20 bmj.jn. (51317)

21 "new england journal of medicine".jn. (63970)

22 (lancet or lancet oncology).jn. (122984)

23 journal of surgical oncology.jn. (6469)

24 cancer radiotherapie.jn. (1278)

25 breast cancer research.jn. (1444)

26 british journal of cancer.jn. (19401)

27 cancer.jn. (35660)

28 international journal of radiation oncology biology physics.jn. (17209)

29 journal of clinical oncology.jn. (17699)

30 radiotherapy & oncology.jn. (4844)

31 head & neck.jn. (3024)

32 or/18-31 (433123)

33 17 and 32 (764)

34 ("20090329" or "20090330" or "20090331").ed. (11698)

35 (200904* or 200905* or 200906* or 200907* or 200908* or 200909* or 200910* or 200911* or 200912*).ed. (584464)

36 (2010* or 2011*).ed. (1722705)

37 or/34-36 (2318867)

38 33 and 37 (199)

Database: EMBASE

Time period covered by the search: 2009 to 2011 Week 33

1 exp "head and neck tumor"/ (178165)

2 (larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or oral or paranasal or para-nasal or nasal or sinus or salivary or parotid).ti,ab. (701393)

3 (neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or adenocarcinoma or carcinoma).ti,ab. (1911349)

4 ("occult primary" or "unknown primary").ti,ab. (2895)

5 2 and (3 or 4) (115654)

6 1 or 5 (242804)

7 exp computer assisted radiotherapy/ (5425)

8 (IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT").ti,ab. (5962)

9 (intensity and modulated).ti,ab. (7067)

10 (conformal or proton or protons).ti,ab. (77792)

11 exp proton/ (21377)

12 or/7-11 (95881)

13 6 and 12 (3217)

14 limit 13 to human (2610)

15 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (35832)

16 "annals of internal medicine".jn. (26018)

17 (bmj or bmj clinical research ed).jn. (26370)

18 "new england journal of medicine".jn. (36002)

19 (lancet or lancet oncology).jn. (114214)

20 ("journal of surgical oncology" or "journal of surgical oncology supplement").jn. (6455)

21 cancer radiotherapie.jn. (1233)

22 breast cancer research.jn. (1043)

23 "british journal of cancer".jn. (18186)

24 cancer.jn. (32101)

25 international journal of radiation oncology biology physics.jn. (19559)

26 ("journal of clinical oncology" or "journal of clinical oncology official journal of the american society of clinical oncology").jn. (27053)

27 "radiotherapy and oncology".jn. (8740)

28 head neck.jn. (114)

29 or/15-28 (352920)

30 14 and 29 (730)

31 (2009* or 2010* or 2011*).em. (2826561)

32 30 and 31 (255)

Database: Cochrane Central Register of Clinical Trials

Time period covered by the search: 2009 - August 22, 2011

#1	MeSH descriptor Head and Neck Neoplasms explode all trees
#2	(larynx or laryngeal or supraglottic or glottic or subglottic or pharynx or pharyngeal or hypopharynx or hypopharyngeal or hypo-pharynx or hypo-pharyngeal or oropharynx or oropharyngeal or oro-pharynx or oro-pharyngeal or nasopharynx or nasopharyngeal or naso-pharynx or naso-pharyngeal or lip or lips or oral or paranasal or para-nasal or nasal or sinus or salivary or parotid):ti,ab,kw
#3	(neoplasm or neoplasms or tumor or tumors or tumour or tumours or cancer or cancers or adenocarcinoma or carcinoma):ti,ab,kw
#4	("occult primary" or "unknown primary"):ti,ab,kw
#5	(#2 AND (#3 OR #4))
#6	(#1 OR #5)
#7	MeSH descriptor Radiotherapy, Conformal explode all trees
#8	(IMRT or 3dcrt or "3D-CRT" or "3-D CRT" or "3D CRT"):ti,ab,kw
#9	(intensity and modulated):ti,ab,kw
#10	(conformal or proton or protons):ti,ab,kw
#11	MeSH descriptor Protons explode all trees
#12	(#7 OR #8 OR #9 OR #10 OR #11)
#13	(#6 AND #12)
#14	(#13), from 2009 to 2011 (24 records)

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) denotes findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B - continued

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?						
Nutting 2011 PARSPORT[7]	RCT	94 pts with pharyngeal squamous-cell carcinoma (T1-T4, N0-N3, M0); mean age: 58 yrs; female: 28%	IMRT (n=47; 60-65 Gy) vs. 3DCRT (n=47; 65 Gy)	4 wks	Late xerostomia, QOL, survival	Late xerostomia OR=0.08 (0.02, 0.31) (IMRT>3DCRT) QOL MD=11.1 (-9.0, 31.2) (IMRT=3DCRT)
Dirix 2010a[11]	Non-RCT	81 post-operative pts with sinonasal or nasal cavity cancer; mean age: 62 yrs; female: 16%	IMRT (n=40; 60-66 Gy) vs. 3DCRT (n=41; 60-66 Gy)	2 yrs	Tumor control, survival, harms	Late xerostomia 12.8% vs. 34.2%, p=0.03 (IMRT>3DCRT) Harms 2.5% vs. 97.6%, p<0.003 mucositis 37.5% vs. 90.2%, p<0.001 xerostmia 75% vs. 97.6%, p<0.003 dermatitis (IMRT>3DCRT)
Dirix 2010b[10]	Non-RCT	97 pts with primary tumor of the oral cavity, oropharynx, larynx, or hypopharynx with majority in stage 4, treated with chemotherapy (cisplatinum 100 mg/m^2) at wk 1 and 4; mean age: 56 yrs; female: 17.5%	IMRT (n=42; 72 Gy) vs. 3DCRT (n=55; 72 Gy)	6 wks	Tumor control, survival, harms	Late xerostomia 52.9% vs. 90.2, p<0.001 (IMRT>3DCRT) Harms 54.7% vs. 72.7%, p<0.007 mucositis 81.0% vs. 92.7%, p<0.08 xerostmia (IMRT>3DCRT)
Chen 2011[8]	Non-RCT	51 pts with squamous-cell carcinoma of the head and neck involving	IMRT (n=27; 70 Gy) vs. 2DRT (n=24; 60-66 Gy)	NR	Late xerostomia, harms, Survival, tumor control	Late xerostomia 11% vs. 58%, p<0.001 (IMRT > 2DRT)

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
		the cervical lymph nodes (N1-N3); median age: 60 yrs; female: 31%				Harms 28% vs. 12%, p=0.01 mucositis (IMRT < 2DRT)
Fang 2010[6]	Non-RCT	356 pts with nasopharyngeal carcinoma (T1-T4); median age: 47 yrs; female: 28.1%	IMRT (n=84; up to 64.8-75.6 Gy) vs. 2DRT (n=106; up to 64.8-75.6 Gy) vs. 3DCRT (n=58; up to 64.8-75.6 Gy) vs. 2DRT+3DCRT boost (n=108; up to 64.8-75.6 Gy)	2.5 yrs (IMRT and 3DCRT), 7.5 yrs (2DRT with or without 3DCRT boost)	QOL	QOL 62.6 vs. 55.9, p>0.05 (IMRT = 3DCRT) 62.6 vs. 49.5, p<0.05 (IMRT > 2DRT) 55.9 vs. 49.5, p>0.05 (3DCRT = 2DRT)
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?						
Nutting 2011 PARSPORT[7]	RCT	94 pts with pharyngeal squamous-cell carcinoma (T1-T4, N0-N3, M0); mean age: 58 yrs; female: 28%	IMRT (n=47; 60-65 Gy) vs. 3DCRT (n=47; 65 Gy)	4 wks	Late xerostomia, QOL, survival	Survival (2 yr) HR=0.68 (0.34, 1.37) RD=2% (-20.0, 16.0) (IMRT=3DCRT)
Dirix 2010a[11]	Non-RCT	81 post-operative pts with sinonasal or nasal cavity cancer; mean age: 62 yrs; female: 16%	IMRT (n=40; 60-66 Gy) vs. 3DCRT (n=41; 60-66 Gy)	2 yrs	Tumor control, survival, harms	Survival (2 yr) 89% vs. 73%, p=0.07 (IMRT=3DCRT) Tumor control 76% vs. 67%, p=0.06 (local) 89% vs. 89%, p=0.68 (distant) (IMRT=3DCRT)
Dirix 2010b[10]	Non-RCT	97 pts with primary tumor of the oral cavity, oropharynx, larynx, or hypopharynx with	IMRT (n=42; 72 Gy) vs. 3DCRT (n=55; 72 Gy)	6 wks	Tumor control, survival, harms	Survival (2 yr) 56% vs. 73%, p=0.29 (IMRT=3DCRT)

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
		majority in stage 4, treated with chemotherapy (cisplatinum 100 mg/m^2) at wk 1 and 4; mean age: 56 yrs; female: 17.5%				Tumor control 81% vs. 66%, p=0.38 (local) 61% vs. 73%, p=0.13 (distant) (IMRT=3DCRT)
Chen 2010[9]	Non-RCT	130 pts with nonmetastatic squamous-cell carcinoma of the oral cavity, oropharynx, larynx/hypopharynx (T1-T4, N0-N3); concurrent chemotherapy: 63%; median age: 61 yrs; female: 41%	IMRT (n=52; 60-66 Gy) vs. 2DRT (n=78; 60-66 Gy)	NR	Survival, tumor control	Survival (3 yr) 72% vs. 69%, p=0.49 (IMRT = 2DRT) Tumor control (3 yr) 73% vs. 70%, p=0.33 (local) (IMRT = 2DRT)
Chen 2011[8]	Non-RCT	51 pts with squamous-cell carcinoma of the head and neck involving the cervical lymph nodes (N1-N3); median age: 60 yrs; female: 31%	IMRT (n=27; 70 Gy) vs. 2DRT (n=24; 60-66 Gy)	NR	Late xerostomia, harms, Survival, tumor control	Survival (2 yr) 87% vs. 86%, p=0.43 (IMRT=2DRT) Tumor control (2 yr) 92% vs. 87%, p=0.44 (local) (IMRT=2DRT)
Lai 2011[5]	Non-RCT	1276 pts with nonmetastatic nasopharyngeal carcinoma (T3-T4, N2-N3); median age: 45 yrs; female: 24%	IMRT (n=512; 54-64 Gy) vs. 2DRT (n=764; 68-76 Gy)	NR	Survival, tumor control	Survival (5 yr) 75.9% vs. 71.4%, p=0.088 (IMRT=2DRT) Tumor control (5 yr) 92.7% vs. 86.8%, p=0.007 (local) (IMRT > 2DRT)
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?						
Lai 2011 [5]	Non-RCT	1276 pts with	IMRT (n=512; 54-64	NR	Survival, tumor	Survival (5 yr)

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration	Outcome	Findings
		nonmetastatic nasopharyngeal carcinoma (T3-T4, N2-N3); median age: 45 yrs; female: 24%	Gy) vs. 2DRT (n=764; 68-76 Gy)		control	In T1 stage patients 100% vs. 94.4%, p=0.016 (IMRT > 2DRT)
Key question 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?						
No studies	NA	NA	NA	NA	NA	NA
IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy; RCT=randomized controlled trial; QOL=quality of life; T=tumor; M=metastasis; N=node; wk(s)=week(s); HR=hazard ratio; RD=risk difference; pts=patients; yr(s)=years; NR=not reported						

Appendix D: Questionnaire Matrix

Comparative Effectiveness and Safety of Radiotherapy Treatments for Head and Neck Cancer
AHRQ Publication No. 10-EHC014-EF May 2010

Access to full report:
http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=447
Clinical expert name: Avraham Eisbruch

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?			
The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute	yes	no	The randomized study (Nutting et al) has been published (Lancet Oncol 2011)

dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent. Quality of life was reported in three observational studies and generally favored IMRT in domains primarily related to xerostomia, such as dry mouth, swallowing, and sticky saliva			
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?			
No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias	yes	no	
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?			
No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
Key question # 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?			
No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy			

Clinical expert name: Bernd Esche

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?			
The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent. Quality of life was reported in three observational studies and generally favored IMRT in domains primarily related to xerostomia, such as dry mouth,	yes	no	

swallowing, and sticky saliva			
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?			
No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias	yes	no	
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?			
No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
Key question # 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?			
No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy			

Clinical expert name: Libni Eapen

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question # 1: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding adverse events and quality of life?			
The strength of the body of evidence is moderate for IMRT reducing late xerostomia and improving quality-of-life domains related to xerostomia compared with 3DCRT. In a randomized, controlled trial presented at a conference but not yet published, the risk difference of late xerostomia grade 2 or higher was 35 percentage points with a 95 percent confidence interval between 12.6 and 55.5 percentage points. There is insufficient detail about methods used in the yet-to-be published randomized trial, so it is difficult to assess its quality and contribution to the overall body of evidence. The six observational studies that reported late xerostomia all favored IMRT. Of the five studies that reported frequencies, the reported range of differences is 7 to 79 percentage points. The strength of evidence is insufficient to draw conclusions about the comparative effects of IMRT and 3DCRT for other adverse events. Acute xerostomia, acute mucositis, late mucositis, acute dysphagia, late skin toxicity, late osteoradionecrosis, and bone toxicity were reported in some and typically favored IMRT, but differences were not consistently statistically significant. Among studies of acute skin toxicity, neither the size of the difference nor the direction was consistent. Quality of life was reported in three observational studies and generally favored IMRT in domains	yes	no	

primarily related to xerostomia, such as dry mouth, swallowing, and sticky saliva			
Key question # 2: What is the comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy regarding tumor control and patient survival?			
No conclusions on tumor control or survival can be drawn from the body of evidence comparing IMRT versus 3DCRT. The single randomized, controlled trial had too small of a sample size and too short of a followup to ascertain differences in tumor control or survival. The strength of the body of evidence for tumor control and patient survival is insufficient. Estimating between-group differences in disease-specific and overall survival is complex and requires greater controls for confounding and bias	yes	no	
Key question # 3: Are there differences in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy for specific patient and tumor characteristics?			
No conclusions can be reached on how patient and tumor characteristics affect outcomes, or on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
Key question # 4: Is there variation in comparative effectiveness of IMRT, 3DCRT, 2DRT, and proton beam therapy because of differences in user experience, target volume delineation, or dosimetric parameters?			
No conclusions can be reached on how radiotherapy or physician characteristics affect outcomes. The strength of evidence is insufficient as no comparative studies addressed these key questions	yes	no	
CER=comparative effectiveness review; IMRT=intensity-modulated radiotherapy; 3DCRT=3-dimentional conformal radiotherapy; 2DRT= 2-dimentional radiotherapy			

Appendix A-3: Example of a "High" Priority Assessment

AHRQ Comparative Effectiveness Review Surveillance Program

CER #13:
Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

Original release date:
February 2008

Surveillance Report:
May 2012

Key Findings:
- The PIVOT trial was identified, making many of the existing key conclusions out of date.
- Key questions 1, 2, and 4 were found to be out of date.
- No significant safety concerns were identified.

Summary Decision

This CER's priority for updating is **High**

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Contents

Table

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer

1. Introduction

Comparative Effectiveness Review (CER) #13, Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer, was released in February 2008.[1] It was therefore due for a surveillance assessment in August, 2008 but the Surveillance program did not exist at that time. Therefore, it is now undergoing its first assessment.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search of Pubmed® for the years 2007-March 5, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Cancer, Journal of Urology, Journal of the National Cancer Institute, Journal of Clinical Urology, and European Urology). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 6 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; the project lead and five subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table (Appendix B), we assessed whether the new findings provided a signal according

to the Ottawa Method or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment 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 reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

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.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

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)?

3. Results

3.1 Search

The literature search identified 1,458 titles. After title and abstract review, we further reviewed the full text of 25 journal articles. The remaining 1,433 titles were rejected because they were editorials, letters, or did not include topics of interest. Sixteen additional articles and one conference proceeding were reviewed at the suggestion of the experts.

Thus, through literature searches and expert recommendations, 41 articles and one conference proceeding went on to full text review. Of these, 20 articles were rejected because they did not answer a key question or did not include a comparison of interest. Thus, 21 articles and one conference proceeding were abstracted into an evidence table (Appendix B).[4-25]

3.2 Expert Opinion

Two of the three experts agreed that KQ1 and KQ2 were out of date. All three experts agreed that KQ4 was out of date. Two of the three experts agreed that KQ3 was still valid.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?				
No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects. Additional randomized controlled trials (RCTs) are needed.				
Randomized comparisons across primary treatment categories				
Radical prostatectomy compared with watchful waiting (2 RCTs). Compared with men who used watchful waiting (WW), men with clinically localized prostate cancer detected by methods other than PSA testing and treated with	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association last May. The study showed no disease-specific survival for surgery vs. watchful waiting. However, a	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific and overall mortality appears to be limited to men under 65 years of age but is not dependent on baseline PSA level or histologic grade. Two RCTs compared WW with RP. The Scandinavian Prostate Cancer Group (SPCG) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent), disease-specific deaths (10 vs. 15 percent), and distant metastases (14 vs. 23 percent) for subjects treated with RP than for subjects assigned WW after a median follow-up of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction than WW. An older trial of 142 men found no significant differences in overall survival between RP and WW after a median follow-up of 23 years, although small sample size limited study power.	subgroup analysis suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit			
Radical prostatectomy vs. external beam radiotherapy (1 RCT). One small (N=106), older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing.	No new data	Not reported	2 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Treatment failure at 5 years of follow-up, defined as acid phosphatase elevation on two consecutive follow-up visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation, occurred in 39 percent for EBRT compared with 14 percent for RP.				
Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high-intensity focused ultrasound (HIFU), proton beam radiation therapy, or intensity modulated radiation therapy (IMRT) (0 RCTs). It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because these options have not been evaluated in RCTs.	1 study (Donnelly) showed no statistical difference between external beam radiotherapy and cryoablation.	Not reported	2 experts thought this was still supported by the literature. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Randomized comparisons within primary treatment categories				
Radical prostatectomy combined with neoadjuvant androgen deprivation therapy (5 RCTs). The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs. One small RCT comparing RP alone and RP combined with neoadjuvant ADT found no overall or disease-specific survival benefit with the addition	No new data	Not reported	3 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
of neoadjuvant ADT after a median follow-up of 6 years. The addition of neoadjuvant ADT did not prevent biochemical progression compared with RP alone in any of the four trials. The trial comparing 3 months and 8 months neoadjuvant ADT with RP reported greater AEs in the 8-month group than the 3-month group (4.5 percent vs. 2.9 percent) and higher incidence of hot flashes (87 percent vs. 72 percent).				
External beam radiotherapy: comparison of EBRT regimens (5 RCTs). No RCTs compared EBRT and WW. It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding brachytherapy) improves overall or disease specific survival compared with other therapies. No EBRT regimen, whether conventional, high dose conformal, dose fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality. Increasing the total amount of radiation or adding brachytherapy after EBRT decreased cancer recurrence compared with lower doses of radiation. One trial (N=936) found that the probability of biochemical or clinical progression at 5 years was lower in the long-arm group (66 Gy in 33 fractions) than the	A systematic review (Bannuru) that evaluated radiation treatments and concluded that the lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer. 1 study (Kuban) reported that moderate dose escalation (78 Gy) decreases biochemical and clinical failure as well as prostate cancer deaths in patients with pretreatment PSA >10 ng/mL or high-risk disease. 1 meta-analysis (Viani) concluded that high dose radiotherapy is superior to conventional dose radiotherapy in preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients, suggesting that this should be offered as a treatment for all patients, regardless of their risk	Not reported	1 expert opinion did not know. 2 experts thought this was out of date.	Original conclusion is probably/possibly out of date and this portion of the original report may need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
short-arm group (52.5 Gy in 20 fractions). Conventional dose EBRT (64 Gy in 32 fractions) and hypofractionated EBRT (55 Gy in 20 fractions) resulted in similar PSA relapse. One trial (N=104) found that brachytherapy combined with EBRT reduced biochemical or clinical progression compared with EBRT alone. One trial (N=303) found that high-dose EBRT (79.2 Gy that included 3D conformal proton 50.4 Gy with 28.8 Gy proton boost) was more effective than conventional-dose EBRT (70 Gy that included 19.8 Gy proton boost) in the percentage of men free from biochemical failure at 5 years (80 percent in the high-dose group and 61 percent in the conventional-dose group). Effectiveness was evident in low-risk disease (PSA <10 ng/ml, stage ²T2a tumors, or Gleason ²6) and higher risk disease. Acute combined gastrointestinal (GI) and genitourinary (GU) toxicity was lower in the long arm (7.0 percent) than in the short arm (11.4 percent). Late toxicity was similar. There were no significant differences between conventional and hypofractionated EBRT with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group. Acute GI or GU symptoms of at least	status. 1 study (Hoskin) found relapse free survival was higher in patients treated with EBRT + high-dose-rate brachytherapy p=0.04. 1 study (Arcangeli) found that hypofractionated was superior in freedom from biochemical failure compared to conventional fractionation in patients with high-risk prostate cancer. 1 study (Pollack) found no difference between conventional and hypofractionated radiotherapy.			

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
moderate severity were similar in the trial comparing high and conventional doses.				
External beam radiotherapy combined with androgen deprivation therapy compared with EBRT alone (3 RCTs). ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score (PSA >10 ng/ml or Gleason >6). One RCT (N=216) found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median follow-up of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone. One RCT (N=206) found that 6 months of ADT + EBRT did not significantly reduce disease-specific mortality compared with conformal EBRT alone in T2b and T2c subjects after a median follow-up of 5.9 years. Six months of combination therapy reduced clinical failure, biochemical failure, or death from any cause compared with EBRT alone in subjects with T2c disease but not in T2b subjects.	1 new RCT (Warde) compared the addition of EBRT to ADT and found that this combination improved overall survival at 7 years compared to ADT alone. 1 RCT (Jones) showed that ADT + EBRT reduced prostate-cancer mortality only among intermediate-risk, but not low-risk, patients through 9 years of follow up. 1 RCT (Hanks) showed no statistical difference between patients treated with an additional 24 months of androgen deprivation therapy compared to a standard short term androgen deprivation with radiotherapy. 1 abstract (Mottet) showed that the addition of local radiotherapy to androgen deprivation therapy reduced the risk of clinical progression. 1 abstract (Bolla) showed that survival with 6 months of androgen deprivation therapy after radiotherapy was significantly shorter than with 3 years of androgen deprivation therapy. 1 study (Widmark) showed the addition of local radiotherapy to endocrine treatment reduced the	Not reported	1 expert opinion did not know. 2 experts thought this was out of date.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	prostate cancer mortality.			
Different doses of adjuvant external beam radiotherapy combined with brachytherapy (1 RCT). One small trial comparing different doses of supplemental EBRT, 20 Gy (N=83) vs. 44 Gy (N=76), adjuvant to brachytherapy (103Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years.	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.
Brachytherapy compared with brachytherapy (1 RCT). No RCTs compared brachytherapy alone with other major treatment options. Preliminary results from one small trial (N=126) comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined aspersistent bleeding, with ^{125}I.	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.
Bicalutamide combined with standard care: RP, EBRT, or WW (3 RCTs). Androgen deprivation with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality. There was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT at the median follow-up of 5.4 years. Among WW subjects,	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
there were significantly more deaths with bicalutamide compared with placebo. The addition of bicalutamide to standard care did not reduce progression.				
Comparative outcomes data from nonrandomized reports				
Cryosurgery. No randomized trials evaluated cryosurgery, and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.	No new data	Not reported	1 expert did not know.	Original conclusion is still valid and this portion of the original report does not need updating.
Laparoscopic and robotic assisted prostatectomy. Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy from 21 nonrandomized trials and case series. Most originated from centers outside of the United States. Median follow-up was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Reintervention rates were similar. Results from	1 study (Barry) did not show fewer adverse effects following robotic prostatectomy.	Not reported	2 experts thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative time were similar for robotic assisted and open RP. Median length of hospital stay (1.2 vs. 2.7 days) and median length of catheterization (7 vs. 13 days) were shorter after robotic assisted RP than open RP.				
Intensity modulated radiation therapy. There was no direct evidence that IMRT results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.	No new data	Not reported	2 experts did not know. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Proton EBRT. There were no data from randomized trials comparing EBRT using protons vs. conventional EBRT or other primary treatment options. In one randomized trial, men with localized prostate cancer had statistically significantly lower odds of biochemical failure (increase in PSA) 5 years after	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
the higher dose of EBRT with a combination of conformal photon and proton beams without increased risk of adverse effects. Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct evidence that proton EBRT results in better overall or disease-free survival than other therapies.				
High-intensity focused ultrasound therapy. There were no data from randomized trials comparing HIFU with other primary treatment options. Biochemical progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from non-controlled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Follow-up duration was <10 years.	No new data	Not reported	2 experts did not know. 1 expert thought this was out of date.	Original conclusion is still valid and this portion of the original report does not need updating.
Health status, quality of life, and treatment satisfaction. Eight studies of health status and quality of life, including a U.S. population-based survey, were eligible. Bother due to dripping or leaking of urine was more than six fold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. Bother due to	1 article (Johannson) reported on 12-year follow-up QOL data from the SPCG-4 trial and men in both the radical prostatectomy and watchful waiting groups reported higher levels of anxiety than the control group. In a longitudinal analysis of men in SPCG-4 who provided information at two follow-up points 9 years apart, 45%	Not reported	1 expert did not know. 1 expert though this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is possibly out of date and this portion of the original report may need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
bowel dysfunction (4 vs. 5 percent) or sexual dysfunction (47 vs. 42 percent) was similar for RP and EBRT. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was among those treated with RP. Treatment satisfaction was highly correlated with bowel, bladder, and erectile function; general health status; belief that the respondent was free of prostate cancer; and whether cancer treatments limited activity or relationships. More than 90 percent said they would make the same treatment decision again, regardless of treatment received.	allocated radical prostatectomy and 60% allocated watchful waiting reported an increase in number of physical symptoms; 61% allocated radical prostatectomy and 64% allocated watchful waiting reported a reduction in quality of life. 1 article (Cook) found that men receiving brachytherapy scored better in urinary (91.8 v 88.1; p=0.02) and sexual (52.5 v 39.2; p=0.001) domains, and in patient satisfaction (93.6 v 76.9; p=0.001) compared with men receiving radical prostatectomy. 1 study (Malcolm) found that brachytherapy and cryotherapy were associated with higher urinary function compared to open radical and robotic radical prostatectomy. Brachytherapy was associated with higher sexual function compared to open radical prostatectomy, robotic radical prostatectomy and cryotherapy.			
Key Question 2. How do patient characteristics affect outcomes?				
No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association last May. Sub-group analysis did not vary by age, race, Charlson score, or performance status.	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
treatment differences reported in some on randomized studies have not been consistently reported in well powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.				
Key Question 3. How do provider and hospital characteristics affect outcomes?				
Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and	No new data	Not reported	2 experts thought this was still supported by the literature. 1 expert did not know.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
outcomes for brachytherapy, cryotherapy, or EBRT.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.				
Regional variation existed in physician availability, ratio of urologists and radiation oncologists per 100,000 adult citizens, screening practice, incidence, mortality, and treatment selection. The direction of regional variation was not always consistent.	No new data	Not reported	2 experts did not know.	Original conclusion is still valid and this portion of the original report does not need updating.
Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the adjusted relative risk of surgery-related complications was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay	No new data	Not reported	2 experts did not know. 1 expert thought this was still supported by the literature.	Original conclusion is still valid and this portion of the original report does not need updating.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
was shorter in patients operated on by surgeons who performed more RPs per year. Surgeon volume of robotic laparoscopic RP was marginally associated with lower adjusted odds of extensive (but not any or focal) positive margins. Pooled analysis showed that surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality.				
Key Question 4. How do tumor characteristics affect outcomes?				
Little data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high risk tumors.	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association last May. A subgroup analysis suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit.	Not reported	3 experts thought this was out of date.	Original conclusion is out of date.
Secondary analysis of one randomized trial concluded that disease-specific mortality at 10 years for men having RP compared with WW differed according to age but not baseline PSA level or Gleason score.	The Prostate Intervention versus Observation Trial (PIVOT) trial results were presented by Dr. Timothy Wilt at the American Urology Association last May. A subgroup analysis did not find that younger men benefited from surgery, though did not look at the interaction between age and tumor-risk.	Not reported	2 experts thought this was out of date. 1 expert thought this was still supported by the literature.	Original conclusion is out of date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.	No new data	Not reported	1 expert did not know. 1 expert thought this was out of date. .	Original conclusion is still valid and this portion of the original report does not need updating.

ADT = androgen deprivation therapy; AE = adverse effects; EBRT = external beam radiotherapy; GnRH = gonadotropin-releasing hormone; Gy = gray; IMRT = intensity modulated radiation therapy; mL = milliliters; ng = nanogram; PSA = prostate specific antigen; RCT = randomized controlled trial; RP = radical prostatectomy; SCEPC = Southern California Evidence-based Practice Center; SPCG = Scandinavian Prostate Cancer Group; WW = watchful waiting

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

ALL SEARCHES WERE LIMITED TO THE FOLLOWING JOURNALS:
Annals of Internal Medicine
BMJ
JAMA
Lancet
New England Journal of Medicine

Cancer
Journal of Urology
Journal of the National Cancer Institute
Journal of Clinical Urology (0 hits)
European Urology

KEY QUESTION 1-
SEARCH 1:
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed® – 2007-3/5/2012

LANGUAGE:
English

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
ultrasound, high-intensity focused, transrectal OR radiotherapy, intensity-modulated OR radiotherapy OR proton OR cryosurgery OR (laparoscopy AND prostatectomy) OR (robotic* AND prostatectomy) OR (transrectal AND ultrasound) OR radiotherap* OR cryosurg* OR (laparoscop* AND prostatectom*) OR therapy[ti] OR therapies[ti] OR treatment*[ti] OR treating[ti] OR treat[ti] OR therapy/mh
AND
Limits: Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV
NOT
metasta*[ti]
NOT
review OR case report* OR case-report* OR letter OR editorial
NOT
animal* NOT (human OR humans)

SEARCH STRATEGY #2:
prostatic neoplasms OR "prostate cancer"
AND
radical prostatectom* OR brachytherap* OR "adjuvant androgen deprivation" OR bicalutamide
AND
Limits: Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV

SEARCH STRATEGY #3:
prostatic neoplasms OR "prostate cancer"
AND
Limits: Meta-Analysis
OR
prostatic neoplasms OR "prostate cancer"
AND
systematic[sb]
NOT
Results of previous searches

SEARCH STRATEGY #4:
prostatic neoplasms OR "prostate cancer"
AND
“quality of life" OR quality of life[mh] OR qol OR hrqol OR "health status" OR satisfaction OR satisfied OR or dissatisf*
NOT
animal* NOT (human OR humans)
NOT
Results of previous searches

TOTAL OF ALL KEY QUESTION 1 SEARCHES AFTER LIMITING TO SPECIFIED JOURNALS: 473

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KEY QUESTION 2-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/7/2012

LANGUAGE:
English

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"

AND
"age factors"OR age [ti] OR ethnicityOR ethnic groups OR race OR racial OR co-morbidit* OR comorbid*

NUMBER OF RESULTS AFTER REMOVING DUPLICATES & REFERENCES TO METASTATIC CANCER & LIMITING TO SPECIFIED JOURNALS: 267

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KEY QUESTION 3-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/12/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
"hospital volume" OR "surgeon volume" OR "clinical competence" OR "physician's practice patterns" OR practice pattern* OR "health services research" OR "learning curve" OR malpractice OR physician*[ti] OR physicians[mh] OR hospital*[ti] OR hospitals[mh] OR epidemiology[mh] OR epidemiolog*[ti]

KEY QUESTION 3 revision (adding term "Case load")
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/13/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
caseload* OR case load* OR case volume*

NUMBER OF RESULTS AFTER REMOVING DUPLICATES & LIMITING TO SPECIFIED JOURNALS: 38

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KEY QUESTION 4-
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2007-3/9/2012

SEARCH STRATEGY:
prostatic neoplasms OR "prostate cancer"
AND
prostate-specific antigen OR "tumor characteristics" OR "tumor volume" OR "tumour characteristics" OR "tumour volume" OR histologic OR histology OR psa OR gleason

AND
mortality[ti] OR mortality[mh] OR survival[ti] OR survival[mh] OR prognos*[ti] OR prognos*[mh] OR outcome*[ti] OR treatment outcome[mh] OR dying OR died OR death OR predict*[ti]
NOT
animal* NOT (human OR humans)

NUMBER OF RESULTS IN SPECIFIED JOURNALS: 683

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TOTAL NUMBER OF RESULTS IN SPECIFIED JOURNALS FOR ALL KEY QUESTIONS: 1458

Appendix B. Evidence Table

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?						
Randomized comparisons across primary treatment categories						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality (HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03).
Randomized comparisons within primary treatment categories						
Warde, 2011[8]	--	n =1201	Locally advance (T3 or T4) prostate cancer, organ confined disease (T2) with a PSA >40 ng/mL, or PSA > 20 ng/mL and a Gleason ≥8	Overall survival	7 years	The addition of radiation therapy to androgen deprivation therapy improved overall survival at 7 years (74%, 95% CI 70– 78 *vs* 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033).
Jones, 2011[9]	--	EBRT alone: n= 992 EBRT + ADT: n = 987	T1b, T1c, T2a, or T2b prostate adenocarcinoma and a PSA level ≤ 20 ng /mL	Overall survival	Median follow-up 9.1 years	Overall survival was 62% among patients receiving EBRT + ADT, as compared with 57% among patients receiving EBRT alone (hazard ratio for death with radiotherapy alone, 1.17;

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						P=0.03). Reanalysis according to risk showed reductions in overall and disease-specific mortality primarily among intermediate-risk patients, with no significant reductions among low-risk patients.
Hanks, 2003[21]	Radiation Therapy Oncology Group (RTOG) Protocol 92-02	n =1554	T2c-4 prostate cancer treated with androgen deprivation therapy, radiotherapy and either no additional therapy or 24 months of androgen deprivation therapy	Overall survival	5 years	No statistical difference in overall survival p=0.73.
Banniru, 2011[11]	--	n = 75 studies	Published English-language comparative studies involving adults with localized prostate cancer who either had first-line radiation therapy or received no initial treatment	Clinical and biochemical out-comes of radiation therapies for localized prostate cancer.	--	75 studies (10 randomized, controlled trials [RCTs] and 65 nonrandomized studies) met the inclusion criteria. A lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer.
Mottet, 2010[22]	--	N = 263 Androgen deprivation therapy: n = 130 Androgen deprivation therapy + radiotherapy: n = 133	Histologically confirmed PCa, T3- 4, or pT3 (biopsy) N0, M0 were treated with androgen deprivation therapy with or without the addition of localized radiotherapy	Progression free survival	5 years	The cumulative incidence of loco-regional progression at 5 years was 9.7% (combined group) versus 29% (ADT group) (p<0.0002) and the cumulative incidence of metastatic progression at 5 years respectively 3% vs 10.8% (p<0.018).
Bolla, 2008[24]	EORTC 22961	n = 970 Short androgen deprivation therapy: n = 483 Long androgen deprivation therapy: n = 487	T1c-2b N1-2 or pN1-2, or T2c-4 N0-2 M0	Overall survival and progression free survival.	Median follow-up 6.4 years	Survival with 6 months of androgen deprivation therapy was significantly shorter than with 3 years of adjuvant androgen deprivation therapy.
Widmark, 2009[14]	--	n = 875	T3; PSA<70; N0; M0	Prostate cancer	Median follow-up	Addition of local radiotherapy

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
		Endocrine treatment only: n = 439 Endocrine treatment and radiotherapy: n = 436		specific mortality	7.6 years	to endocrine treatment halved the 10-year prostate-cancer-specific mortality.
Kuban, 2011[17]		n= 301	T1b-T3 prostate cancer treated to 70 Gy vs 78 Gy of radiation therapy.	Incidence of death from prostate cancer versus other causes.	9 years	Moderate dose escalation (78 Gy) decreases biochemical and clinical failure as well as prostate cancer death in patients with pretreatment PSA >10 ng/mL or high-risk disease.
Viani, 2009[18]	--	Total patient population = 2812; 7 studies included	Randomized, controlled studies comparing high dose radiation therapy with conventional dose radiation therapy for localized prostate cancer.	Biochemical failure, all-cause mortality rate, and prostate cancer mortality rate.	--	High dose radiotherapy is superior to conventional dose radiotherapy in preventing biochemical failure in low-, intermediate-, and high-risk prostate cancer patients p<0.001.
Hoskin, 2012[19]	--	n = 218 EBRT: n = 108 EBRT + high-dose-rate brachytherapy boost: n = 110	Stage T1 to T3, with no evidence of metastatic disease, a PSA <50 ug/l.	Relapse free survival	Median follow-up 85 months	Relapse free survival was higher in patients treated with EBRT + high-dose-rate brachytherapy p=0.04
Arcangeli, 2010[20]	--	n = 168	High risk patients that received 9 months of androgen deprivation therapy.	Freedom from biochemical failure.	Median follow-up for hypofractionated group: 32 months; median follow-up for conventional fractionation: 35 months.	Hypofractionated was superior in freedom from biochemical failure compared to conventional fractionation in patients with high-risk prostate cancer.
Pollack, 2011[23]	--	n = 303 Conventional: n = 152 Hypofractionated: n = 151	Age 65 years or older and were diagnosed with prostate cancer from 1995 to 2005 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database.	Biochemical failure	Median follow-up 60 months	No statistically significant differences between the treatment arms for biochemical failure, any failure, or late side effects.

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Donnelly, 2010[13]	--	n = 244 Cryoablation: n = 122 EBRT: n = 122	Eligibility criteria: histologically proven adenocarcinomaof the prostate, a biopsy tumor classification ofT2 or T3, no evidence of lymph node or distant metastases, a pretreatment PSA level#20 ng/mL, and a gland volume #60 cm3	Disease progression	36 months	No statistically significant disease progression.
Comparative outcomes data from nonrandomized reports						
Hu, 2009[4]	--	Minimally-invasive prostatectomy: n = 1938 Open radical prostatectomy: n = 6899	Population-based cohort study using US Surveillance, Epidemiology, and End Results Medicare linked data from 2003-2007	Postoperative 30-day complications, Anastomotic strictures 31-365 days post-operatively, incontinence, erectile dysfunction, and postoperative use of cancer therapies.	1.5 years	Minimally invasive prostatectomy compared to open radical prostatectomy was associated with shorter length of stay, lower rates of blood transfusions, fewer postoperative respiratory complications, fewer miscellaneous surgical complications, fewer anastomotic strictures, but increased risk of genitourinary complications, increased incontinence, and increased erectile dysfunction.
Keating, 2010[5]	--	n = 37,443	Men diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration from 1/2001-12/2004	Association of androgen deprivation therapy with GnRH agonists, oral antiandrogens, the combo of the two, or orchiectomy with diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, or stroke.	Through 12/2005	Treatment with GnRH agonists was associated with increased risk of diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, and stroke. Combined androgen blockade and orchiectomy were associated with increased risk of coronary heart disease.

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Kibel, 2012[6]	--	Radical prostatectomy: n = 6,485 EBRT: n = 2,264 Brachyotherapy: n = 1,680	Men with localized prostate cancer	Overall survival and prostate specific mortality	10 year	EBRT was associated with decreased overall survival and increased prostate cancer specific mortality compared to radical prostatectomy. Brachytherapy was associated with decreased overall survival compared to radical prostatectomy.
Dosoretz, 2010[7]	--	Brachyotherapy + neoadjuvant hormone therapy: n = 1,083 Brachyotherapy alone: n = 1,391	Men with localized prostate cancer treated between 1991 and 2005 at centers within the 21st Century Oncology Consortium	All cause mortality	Median follow-up: 4.8 years (3.3-7.5)	Men $\geq$ 73 years who received brachytherapy and neoadjuvant hormone therapy had an increased risk of all cause mortality compared to men who only received brachyotherapy.
Johansson, 2011[10]	SPCG-4	Radical prostatectomy: n = 182 Watchful waiting: n = 167 Control: n = 214	All Swedish and Finnish men (400 of 695) assigned to radical prostatectomy or watchful waiting and a population-based control.	Quality of life	Median follow-up of 12.2 years	Anxiety was higher in the radical prostatectomy and watchful waiting groups (77 [43%] of 178 and 69 [43%] of 161 men) than in the control group (68 [33%] of 208 men; relative risk 1·42, 95% CI 1·07–1·88). Prevalence of erectile dysfunction was 84% (146 of 173 men) in the radical prostatectomy group, 80% (122 of 153) in the watchful-waiting group, and 46% (95 of 208) in the control group and prevalence of urinary leakage was 41% (71 of 173), 11% (18 of 164), and 3% (six of 209), respectively. In a longitudinal analysis of men in SPCG-4 who provided information at two follow-up points 9 years apart, 38 (45%) of 85 men allocated radical prostatectomy and 48 (60%) of 80 men allocated watchful waiting reported an increase in

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						number of physical symptoms; 50 (61%) of 82 and 47 (64%) of 74 men, respectively, reported a reduction in quality of life.
Crook, 2011[16]	SPIRIT: Surgical Prostatectomy versus Interstitial Radiation Intervention Trial	n = 168 (60.7% brachytherapy; 39.3% radical prostatectomy)	Men recruited for the SPIRIT trial	Health related quality of life	5 years	No difference in bowel or hormonal domains, but men treated with brachytherapy scored better in urinary (91.8 v 88.1; p=0.02) and sexual (52.5 v 39.2; p=0.001) domains, and in patient satisfaction (93.6 v 76.9; p=0.001).
Malcolm, 2010 [12]	--	n= 785	From February 2000 to December 2008 all patients undergoing operative treatment of localized prostate cancer at UCLA were asked to participate.	Health related quality of life	24 months	Brachytherapy and cryotherapy were associated with higher urinary function compared to open radical and robotic radical prostatectomy. Brachytherapy was associated with higher sexual function compared to open radical prostatectomy, robotic radical prostatectomy and cryotherapy.
Barry, 2012[15]	--	n = 797 Robotic surgery: n = 406 Open surgery: n = 220	Random population sample from Medicare claims	Adverse effects (sexual dysfunction and incontinence)	14 months postoperatively	There were no statistical difference in adverse effects.
Key Question 2. How do patient characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n =364 Observation: n =367	Age $\leq$ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed $\leq$12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
						(HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03)
Key Question 3. How do provider and hospital characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Non-significant absolute risk reduction in patients undergoing radical prostatectomy Adjusted risk ratio 2.9% (-4.1-10.3). Sub-group analysis did not vary by age, race, Charlson score, performance status, or Gleason score, but did vary by PSA and tumor risk. In men with low risk radical prostatectomy did not reduce all-cause mortality (HR = 1.15 p=0.045) but in men with intermediate risk, radical prostatectomy decreased overall mortality (HR = 0.69; p=0.04). In men with PSA >10, radical prostatectomy reduced overall mortality (HR = 0.36, p=0.03).
Key Question 4. How do tumor characteristics affect outcomes?						
Wilt, not yet published, but presented at the American Urological Association 2011 Annual Meeting in Washington, DC[25]	PIVOT Prostate Cancer Intervention Versus Observation Trial	n = 731 Radical prostatectomy: n = 364 Observation: n = 367	Age ≤ 75, T1-2, N0, M0, PSA <50 ng/mL, diagnosed ≤12 months, candidate for radical prostatectomy	All cause mortality	Median follow-up 10 years	Subgroup analyses suggested that men with high-risk features (PSA > 10, and intermediate risk) might have a survival benefit and did not find that younger men benefited from surgery, though did not look at the interaction between age and tumor-risk.

ADT = androgen deprivation therapy; EBRT = external beam radiotherapy; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; mL = milliliters; ng = nanogram; Gy = gray

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer**

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?			
No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decision making. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
and adverse effects. Additional randomized controlled trials (RCTs) are needed.			
Randomized comparisons across primary treatment categories			
Radical prostatectomy compared with watchful waiting (2 RCTs). Compared with men who used watchful waiting (WW), men with clinically localized prostate cancer detected by methods other than PSA testing and treated with radical prostatectomy (RP) experienced fewer deaths from prostate cancer, marginally fewer deaths from any cause, and fewer distant metastases. The greater benefit of RP on cancer-specific and overall mortality appears to be limited to men under 65 years of age but is not dependent on baseline PSA level or histologic grade. Two RCTs compared WW with RP. The Scandinavian Prostate Cancer Group (SPCG) trial found significantly lower incidences of all-cause deaths (24 vs. 30 percent), disease-specific deaths (10 vs. 15 percent), and distant metastases (14 vs. 23 percent) for subjects treated with RP than for subjects assigned WW after a median follow-up of 8.2 years. Surgery was associated with greater urinary and sexual dysfunction than WW. An older trial of 142 men found no significant differences in overall survival between RP and WW after	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
a median follow-up of 23 years, although small sample size limited study power.			
Radical prostatectomy vs. external beam radiotherapy (1 RCT). One small (N=106), older trial indicated that, compared with EBRT, RP was more effective in preventing progression, recurrence, or distant metastases in men with clinically localized prostate cancer detected by methods other then PSA testing. Treatment failure at 5 years of follow-up, defined as acid phosphatase elevation on two consecutive follow-up visits or appearance of bone or parenchymal disease with or without concomitant acid phosphatase elevation, occurred in 39 percent for EBRT compared with 14 percent for RP.	☐	New Evidence:	☐
Cryotherapy, laparoscopic or robotic assisted radical prostatectomy, primary androgen deprivation therapy, high-intensity focused ultrasound (HIFU), proton beam radiation therapy, or intensity modulated radiation therapy (IMRT) (0 RCTs). It is not known whether these therapies are better or worse than other treatments for localized prostate cancer because these options have not been evaluated in RCTs.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Randomized comparisons within primary treatment categories			
Radical prostatectomy combined with neoadjuvant androgen deprivation therapy (5 RCTs). The addition of neoadjuvant hormonal therapy to RP did not improve survival or cancer recurrence rates, defined by PSA recurrence, but increased AEs. One small RCT comparing RP alone and RP combined with neoadjuvant ADT found no overall or disease-specific survival benefit with the addition of neoadjuvant ADT after a median follow-up of 6 years. The addition ofneoadjuvant ADT did not prevent biochemical progression compared with RP alone in any of the four trials. The trial comparing 3 months and 8 months neoadjuvant ADT with RP reported greater AEs in the 8-month group than the 3-month group (4.5 percent vs. 2.9 percent) and higher incidence of hot flashes (87 percent vs. 72 percent).	☐	New Evidence:	☐
External beam radiotherapy: comparison of EBRT regimens (5 RCTs). No RCTs compared EBRT and WW. It is not known if using higher doses of EBRT by increasing either the total amount or type of radiation (e.g., via high-dose intensity modulated or proton beam or by adding brachytherapy) improves overall or disease specific survival compared with other therapies. No EBRT regimen, whether conventional, high dose conformal, dose	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
fractionation, or hypofractionation, was superior in reducing overall or disease-specific mortality. Increasing the total amount of radiation or adding brachytherapy after EBRT decreased cancer recurrence compared with lower doses of radiation. One trial (N=936) found that the probability of biochemical or clinical progression at 5 years was lower in the long-arm group (66 Gy in 33 fractions) than the short-arm group (52.5 Gy in 20 fractions). Conventional dose EBRT (64 Gy in 32 fractions) and hypofractionated EBRT (55 Gy in 20 fractions) resulted in similar PSA relapse. One trial (N=104) found that brachytherapy combined with EBRT reduced biochemical or clinical progression compared with EBRT alone. One trial (N=303) found that high-dose EBRT (79.2 Gy that included 3D conformal proton 50.4 Gy with 28.8 Gy proton boost) was more effective than conventional-dose EBRT (70 Gy that included 19.8 Gy proton boost) in the percentage of men free from biochemical failure at 5 years (80 percent in the high-dose group and 61 percent in the conventional-dose group). Effectiveness was evident in low-risk disease (PSA <10 ng/ml, stage ²T2a tumors, or Gleason ²6) and higher risk disease. Acute combined gastrointestinal (GI) and genitourinary (GU) toxicity was lower in the long arm (7.0 percent) than in the short arm (11.4 percent). Late toxicity was similar. There			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
were no significant differences between conventional and hypofractionated EBRT with the exception of rectal bleeding at 2 years after therapy, which had a higher prevalence in the hypofractionated group. Acute GI or GU symptoms of at least moderate severity were similar in the trial comparing high and conventional doses.			
External beam radiotherapy combined with androgen deprivation therapy compared with EBRT alone (3 RCTs). ADT combined with EBRT (ADT + EBRT) may decrease overall and disease-specific mortality but increase AEs compared with EBRT alone in high-risk patients defined by PSA levels and Gleason histologic score (PSA >10 ng/ml or Gleason >6). One RCT (N=216) found that conformal EBRT combined with 6 months of ADT reduced all-cause mortality, disease-specific mortality, and PSA failure compared with conformal EBRT alone after a median follow-up of 4.5 years. There were significant increases in gynecomastia and impotence in the ADT + EBRT group compared with EBRT alone. One RCT (N=206) found that 6 months of ADT + EBRT did not significantly reduce disease-specific mortality compared with conformal EBRT alone in T2b and T2c subjects after a median follow-up of 5.9 years. Six months of combination therapy reduced clinical failure, biochemical failure, or death from any cause compared with EBRT alone in	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
subjects with T2c disease but not in T2b subjects.			
Different doses of adjuvant external beam radiotherapy combined with brachytherapy (1 RCT). One small trial comparing different doses of supplemental EBRT, 20 Gy (N=83) vs. 44 Gy (N=76), adjuvant to brachytherapy (103Pd) implant found no significant differences in the number of biochemical failure events and freedom from biochemical progression at 3 years.	☐	New Evidence:	☐
Brachytherapy compared with brachytherapy (1 RCT). No RCTs compared brachytherapy alone with other major treatment options. Preliminary results from one small trial (N=126) comparing ^{125}I with ^{103}Pd brachytherapy found similar biochemical control at 3 years. There was a trend toward more radiation proctitis, defined as persistent bleeding, with ^{125}I.	☐	New Evidence:	☐
Bicalutamide combined with standard care: RP, EBRT, or WW (3 RCTs). Androgen deprivation with bicalutamide alone or in addition to RP or EBRT did not reduce cancer recurrence or mortality. There was no difference in total number of deaths between the bicalutamide and placebo groups for men receiving RP or EBRT at the median follow-up of 5.4 years. Among WW subjects, there were significantly more deaths with bicalutamide	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
compared with placebo. The addition of bicalutamide to standard care did not reduce progression.			
Comparative outcomes data from nonrandomized reports			
Cryosurgery. No randomized trials evaluated cryosurgery, and the majority of reports included patients with T3-T4 stages. Overall or prostate-cancer specific survival was not reported. Progression-free survival in patients with T1-T2 stages ranged from 29 to 100 percent. AEs were often not reported but, when described, included bladder outlet obstruction (3 to 21 percent), tissue sloughing (4 to 15 percent), and impotence (40 to 100 percent). Outcomes may be biased by patient and provider characteristics.	☐	New Evidence:	☐
Laparoscopic and robotic assisted prostatectomy. Three reviews estimated the effectiveness and AEs of laparoscopic and robotic assisted prostatectomy from 21 nonrandomized trials and case series. Most originated from centers outside of the United States. Median follow-up was 8 months. Laparoscopic RP had longer operative time but lower blood loss and improved wound healing compared with open retropubic RP. Reintervention rates were similar. Results from eight nonrandomized reports suggested that total complications, continence rates, positive surgical margins, and operative	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
time were similar for robotic assisted and open RP. Median length of hospital stay (1.2 vs. 2.7 days) and median length of catheterization (7 vs. 13 days) were shorter after robotic assisted RP than open RP.			
Intensity modulated radiation therapy. There was no direct evidence that IMRT results in better survival or disease-free survival than other therapies for localized prostate cancer. Based on nonrandomized data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT are comparable with conformal radiation. There is low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.	☐	New Evidence:	☐
Proton EBRT. There were no data from randomized trials comparing EBRT using protons vs. conventional EBRT or other primary treatment options. In one randomized trial, men with localized prostate cancer had statistically significantly lower odds of biochemical failure (increase in PSA) 5 years after the higher dose of EBRT with a combination of conformal photon and proton beams without increased risk of adverse effects. Based on nonrandomized reports, the rates of clinical outcomes and toxicity after proton therapy may be comparable with conformal radiation. There was no direct	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
evidence that proton EBRT results in better overall or disease-free survival than other therapies.			
High-intensity focused ultrasound therapy. There were no data from randomized trials comparing HIFU with other primary treatment options. Biochemical progression-free survival rates of 66 to 87 percent and negative biopsy rates of 66 to 93 percent were reported from noncontrolled studies. The absolute risk of impotence and treatment-related morbidity appeared to be similar to other treatments. Followup duration was <10 years.	☐	New Evidence:	☐
Health status, quality of life, and treatment satisfaction. Eight studies of health status and quality of life, including a U.S. population-based survey, were eligible. Bother due to dripping or leaking of urine was more than six fold greater in RP-treated men than in men treated with EBRT after adjusting for baseline factors. Bother due to bowel dysfunction (4 vs. 5 percent) or sexual dysfunction (47 vs. 42 percent) was similar for RP and EBRT. In a subgroup of men ages 70 and over, bother due to urine, bowel, or sexual dysfunction was 5.1, 2.4, and 2.8 times higher, respectively, for aggressive (RP/EBRT) vs. conservative (WW/ADT) therapy. Satisfaction with treatment was high, with less than 5 percent reporting dissatisfaction, unhappiness, or feeling terrible about their treatment, although the highest percent was	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
among those treated with RP. Treatment satisfaction was highly correlated with bowel, bladder, and erectile function; general health status; belief that the respondent was free of prostate cancer; and whether cancer treatments limited activity or relationships. More than 90 percent said they would make the same treatment decision again, regardless of treatment received.			
Key Question 2. How do patient characteristics affect outcomes?			
No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest treatment differences reported in some on randomized studies have not been consistently reported in well powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
age ranged from a low of 63 years for trials of RP to 72 years for trials of EBRT. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of RP compared with WW may be limited to men under 65 years of age. Practice patterns from observational studies show that RP is the most common treatment option in younger men with localized prostate cancer.			
Key Question 3. How do provider and hospital characteristics affect outcomes?			
Results from national administrative databases and surveys suggested that provider/hospital characteristics, including RP procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and outcomes for brachytherapy, cryotherapy, or EBRT.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Regional variation existed in physician availability, ratio of urologists and radiation oncologists per 100,000 adult citizens, screening practice, incidence, mortality, and treatment selection. The direction of regional variation was not always consistent.	☐	New Evidence:	☐
Surgeon RP volume was not associated with RP-related mortality and positive surgical margins. However, the adjusted relative risk of surgery-related complications was lower in patients treated by higher volume surgeons. Urinary complications and incontinence were lower for patients whose surgeons performed more than 40 RPs per year. The length of hospital stay was shorter in patients operated on by surgeons who performed more RPs per year. Surgeon volume of robotic laparoscopic RP was marginally associated with lower adjusted odds of extensive (but not any or focal) positive margins. Pooled analysis showed that surgery-related mortality and late urinary complications were lower and length of stay was shorter in hospitals that performed more RPs per year. Hospital readmission rates were lower in hospitals with greater volume. Teaching hospitals had a lower rate of surgery-related complications and higher scores of operative quality.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 4. How do tumor characteristics affect outcomes?			
Little data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high risk tumors.	☐	New Evidence:	☐
Secondary analysis of one randomized trial concluded that disease-specific mortality at 10 years for men having RP compared with WW differed according to age but not baseline PSA level or Gleason score.	☐	New Evidence:	☐
Based on very limited nonrandomized trial data, disease-specific survival was similar for men treated with EBRT or with RP in men with baseline PSA >10 ng/ml. Men with Gleason scores 8-10 were more likely to have biochemical recurrence than men with Gleason scores 2-6, regardless of type of treatment.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Appendix B. Methods for Identifying Regulatory Information or Safety Alerts

Objectives

Between May 2011 and August 2012, under contract with the U.S. Agency for Healthcare Research and Quality (AHRQ), the ECRI Institute Evidence-based Practice Center (EPC) assisted the Southern California EPC—RAND Corporation and the Ottawa EPC in updating reports for the Effective Health Care (EHC) Program. ECRI's role in this project was to provide information about alerts and updates on specific drugs, products, and medical devices that might warrant an update for major sections—such as key questions, discussions, and conclusions—of comparative effectiveness reports (CERs) published under the EHC Program since 2008.

Methods

The RAND EPC provided ECRI Institute with a list of targeted CERs published and posted on the EHC Web site since 2008.

ECRI Institute conducted daily Web site surveillance for advisory information from the U.S. Food and Drug Administration (FDA), Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). We monitored these Web sites for their content on drug- and device-related activity, specifically, drug approvals and alerts and device approvals/clearances, safety alerts, and recalls. The drug products and medical devices associated with an alert were cross-checked against the final CERs posted on the EHC Program Web site.

Besides ensuring daily surveillance for identified topics, we performed comprehensive searches for selected reports using ECRI Institute's Health Devices Alerts database. Examples of such reports include: *Radiofrequency Catheter Ablation for Atrial Fibrillation, Diagnosis and Treatment of Obstructive Sleep Apnea,* and *Devices to Remove Thrombus and/or Protect from Distal Embolization in Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention of Native Vessels.*

Final EHC reports that were not included in the initial list were outside the scope of our surveillance activity. However, we did review some excluded CERs for related alerts when specific requests were made by either the RAND or Ottawa EPCs.

Literature Scope

ECRI Institute medical librarians directed the ECRI Institute principal investigator on indexing the conditions and interventions addressed in AHRQ CERs to map to the final EHC reports the drug products and medical devices flagged during surveillance. ECRI Institute research analysts routinely monitored the following resources for drug- and device-related notifications:

ECRI Institute Health Devices Alerts Database (subscription required)
http://members2.ecri.org/Components/Alerts/Pages/login.aspx?Page=ALERTSEARCH

Health Canada—Advisories, Warnings and Recalls
www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php

Medicines and Healthcare products Regulatory Agency (United Kingdom)
www.mhra.gov.uk/index.htm#page=DynamicListMedicines

Medicines and Healthcare products Regulatory Agency—Drug Alerts
www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/DrugAlerts/index.htm

Medicines and Healthcare products Regulatory Agency—Drug Safety Update
www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/

Medicines and Healthcare products Regulatory Agency—Medical Device Alerts
www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/MedicalDeviceAlerts/index.htm

U.S. Food and Drug Administration—CDRH Consumer News
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/consumernew-rss.cfm

U.S. Food and Drug Administration—CDRH Medical Device Recalls since December 20, 2010
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res-rss.cfm

U.S. Food and Drug Administration—CDRHNew
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/cdrhnew-rss.cfm

U.S. Food and Drug Administration—Drug Shortages
www.fda.gov/cder/drug/shortages/drugshortage.xml%20

U.S. Food and Drug Administration—Enforcement Report
www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/EnforcementReports/rss.xml

U.S. Food and Drug Administration—MedWatchSafety Alert RSS Feed
www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/MedWatch/rss.xml

U.S. Food and Drug Administration—Patient Safety News
www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/rss.cfm

U.S. Food and Drug Administration—Press Releases
www.fda.gov/bbs/topics/news/rssPress.xml%20

U.S. Food and Drug Administration—Recalls/Safety Alerts
www.fda.gov/oc/po/firmrecalls/rssRecalls.xml

Data Abstraction and Synthesis

The data abstracted from the regulatory agencies' Web sites were organized in summary tables. ECRI Institute then generated and submitted monthly alert summary reports to the RAND and Ottawa EPCs. Our monthly reports captured drug- and device-related activity reported on the FDA, Health Canada, and MHRA Web sites during the previous month. No newly-approved drug products or medical devices relevant to our list of targeted CERs were identified via our surveillance. The reports submitted to the two EPCs included the following information:

- Drug or device notification and surveillance activity date
- EHC report most likely to be affected by the notification
- Type of notification
- Content of notification as reported by the regulatory agency
- Link (Internet address) to notification
- Any ongoing safety reviews by other organizations
- Description of potential update needed, mapped to the corresponding section of the CER

Drug notifications were reported as:

- *Drug Advisory*
- *Drug Safety Labeling Change*
- *Withdrawal*
- *Drug Safety Communication*

Device notifications were reported as:
Manufacturer and User Facility Device Experience (MAUDE) Adverse Event Report