Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Systematic Review*

Draft review available for public comment from March 29, 2013 to April 26, 2013.

Research Review Citation: Sun F, Oyesanmi O, Fontanarosa J, Reston J, Guzzo T, Schoelles K. Therapies for Clinically Localized Prostate Cancer: Update of a 2008 Systematic Review. Comparative Effectiveness Review No. 146. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2007-10063.) AHRQ Publication No. 15-EHC004-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Published Online: December 16, 2014

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Structured Abstract	Structured abstract pg vi – Bowel incontinence is not a common reported complication of RP.	Structured abstract pg vi – We thank the reviewer for all the additional comments made in this document. We have removed bowel incontinence from the list of harms associated with prostatectomy.
Peer Reviewer 1	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
Peer Reviewer 2	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
Peer Reviewer 3	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
TEP Reviewer 1	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
TEP Reviewer 2	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Executive Summary	Executive summary ES1 Controversial among health care professionals and professional societies – consider including references for AUA, ACS, EAU recommendations The statement "Gleason 6 or lower tumors are considered potentially indolent" is highly controversial. A statement should be included here that biopsy Gleason grade may sometimes underestimate the true Gleason grade of the tumor ES-3 "The key finding of the analysis was that the Prostate Cancer Intervention Versus Observation Trial (PIVOT),14-16 published after the 2008 report, has outdated conclusions." – is this a typographical error? PIVOT's conclusions are not outdated. ES-4 I think it's important to clarify for population that we are dealing with clinical stage, not pathologic stage. It might be worth it to define pathologic stage and to make this clarification earlier in the text to avoid confusion. ES-10 A note should be made about the very short median survival of men in the PIVOT cohort, as well as its failure to accrue its targeted enrollment. ES-16 Include a comment about past radiation therapy using a lower dose than is currently known to be effective. All subgroups inconclusive -- ?rationale	We thank the reviewer for finding the time to review and make suggestions on the report. ES-1 As suggested by another reviewer, we have cited the study by Etzioni et al. 2013,[1] to point out that some experts believe that the U.S. Preventive Services Task Force (USPSTF) report does not give sufficient consideration to the limitations of screening trials on which their recommendations were based. We have also noted that the American Urological Association [AUA]) currently advocates shared decision making regarding prostate-specific antigen (PSA) testing. We have left the statement "Gleason 6 or lower tumors are considered potentially indolent" as it appears in the report with the citation and now included a followup sentence based on the present suggestion that reads "However, biopsy-derived Gleason grade may sometimes underestimate the true Gleason grade of the tumor." ES-3 We have clarified this statement because we were referring to the conclusions in the original 2008 report. ES-4 We stated in the Executive Summary and other sections of the report that the population of interest includes only men with clinically localized prostate cancer. In addition, we included a sentence in the Executive Summary to differentiate between clinical and pathological staging "Staging of prostate cancer could be clinical (based on a digital rectal examination of the prostate gland, prostate biopsy, and laboratory tests) or pathological (based on surgery and examination of resected prostate tissue)." ES-10 We have now included in our Results section both the short medial survival of men in the PIVOT as well as the failure of the study to accrue its targeted enrollment of 2,000 men.

Commentator & Affiliation	Section	Comment	Response
			(continued) ES-16 We have now included that several studies reported using a lower radiation dose than is currently known to be effective. Subgroup analyses were often not pre-specified in the study protocol, were often underpowered to detect differences between treatments, and generally should be considered as hypothesis-generating rather than definitive analyses when they are post hoc.
TEP Reviewer 4	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
TEP Reviewer 5	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
TEP Reviewer 6	Executive Summary	Nice	We thank the reviewer for finding the time to review and make suggestions on the report.
TEP Reviewer 7	Executive Summary		We thank the reviewer for finding the time to review and make suggestions on the report.
Peer Reviewer 1	Introduction	See General comments.	
Peer Reviewer 2	Introduction	Well stated	Thank you.
Peer Reviewer 3	Introduction	The introduction appropriately places the review in context, including identifying important clinical and research issues and addressing the need for an update (publication of PIVOT results, longer-term SPCG-4 results).	Thank you.
TEP Reviewer 1	Introduction	No comments.	
TEP Reviewer 2	Introduction	See General comments section.	
TEP Reviewer 3	Introduction	Very good and clear. Perhaps too much of a focus on the lack of evidence for PSA screening in this document which is meant to focus on treatment of those already with a prostate cancer diagnosis. Pg 1. After declining incidence, should also note declining mortality. Pg. 3 Much clearer discussion of clinical versus pathologic staging. This would be good for the executive summary as well.	Thank you. We provided some background information on PSA screening based on suggestions from other clinical experts and we believe that this information is relevant to this report. Pg. 1 We have now added “decline in mortality” Pg. 3 We have included “staging of prostate cancer could be clinical (based on a digital rectal examination of the prostate gland, prostate biopsy, and laboratory tests) or pathological (based on surgery and examination of resected prostate tissue)” to differentiate between both staging types.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	Introduction	States what it intends to do well.	Thank you
TEP Reviewer 5	Introduction	The results of the 2008 report are summarized and the additional information available to support the timing of this updated analysis are well described. The overall methodology is likewise well summarized.	Thank you.
TEP Reviewer 6	Introduction	Introduction: good background – might have gone into a bit more detail on the 3 prior rct's attempted to compare fundamentally different studies. 1987 trial of XRT vs RP SPIRIT trial in the 1990's the NCIC trial of immediate versus deferred treatment. All failed to accrue	Thank you. We have now added more discussion about the challenges in achieving target enrollments in RCTs.
TEP Reviewer 7	Introduction	Disagree that recommendation against PSA testing is "controversial". No organization (including the AUA) currently recommends PSA testing. At most organizations recommend patients be informed about the low likelihood of benefit (1/1000 or less) and high likelihood of harms, and that no man should be screened without knowledge of this information and then requesting.	We have deleted the term "controversial." We have noted that the American Urological Association [AUA]) currently advocates shared decision making regarding prostate-specific antigen (PSA) testing to our background section.
Peer Reviewer 1	Methods	See general comments.	
Peer Reviewer 2	Methods	The RCT's are limited but appropriately defined. One may wish to qualify that PC death is subject to ascertainment bias and so all cause death which is not subject to ascertainment is a more reliable and robust endpoint. The issue with all cause death is quantifying comorbidity using a validated metric which has not been done to date prior to randomization in any RCT.	We have added these suggestions to the Limitations of the Evidence Base section in the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Methods	P 14. One concern is that observational studies are uniformly considered to be at high-risk for bias because treatment assignment was not random and outcome assessors were not blinded. I think there are important qualitative differences in study validity that are glossed over by these criteria. For example, an observational study that randomly sampled population cohorts and used statistical techniques to adjust for selection bias represents a less-biased design than a single center study that used simple multivariable regression analyses. Lack of blinding is less concerning for studies relying on vital statistics or self-reported quality of life outcomes. Given the challenges in conducting RCT of the various treatment modalities, observational studies potentially have an important role in comparative effectiveness research--which the EHC review systematically downplays.	Thank you for your feedback. Observational studies will always tend to be rated as having a higher risk of bias relative to RCTs. We did rate studies that used instrumental variable analysis as superior to studies that used other statistical methods to adjust for selection bias. Also, the limitations of studies in the evidence base is not the only factor considered in the strength of evidence assessment. Other factors include the consistency of findings across studies, the precision of the effect estimate, and the directness of the evidence in terms of the comparison and outcomes. A strong dose-response relationship and a large magnitude of effect can increase the strength of the evidence, even if it comes from observational studies. We agree that aspects of design of observational studies can improve the risk of bias of individual studies, and that well-designed observational studies have an important role in comparative effectiveness research. We have also revised the future research section in an attempt to provide equal emphasis for RCTs and nonRCTs that are appropriately designed to minimize the risk of selection bias. We believe that information from both study designs may be useful to guide future clinical decisionmaking.
TEP Reviewer 1	Methods	I agree with the inclusion/exclusion criteria and search strategies. Outcomes extracted are appropriate. I have a question about the ratings of risk of bias...see Methods.	Thank you.
TEP Reviewer 2	Methods	See General comments section.	
TEP Reviewer 3	Methods	It seems that a huge number of studies were excluded in order to arrive at the best evidence. While I agree that it is important to perform an analysis of only the best, I think there would be some value to analyzing some of the other studies to see whether there is any particularly important information to be found there. For instance, the 12 RCTs with <100 patients per treatment arm might contain useful information which can be weighted less to reflect the small numbers of patients, without excluding them altogether. Pg. 11 What is the rationale for excluding KQ3 analyses for radiation therapy?	The RCTs you are referring to were excluded for reasons other than sample size. Pg. 11 We included any study that compared RP to another treatment of interest, addressed the KQ and reported efficacy of treatment on a measure of survival. We did not identify any studies since the 2008 report that addressed KQ3.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	Methods	Are the inclusion and exclusion criteria justifiable? No. when only 1% of publications are valid, the rules for the study limit the applicability of the conclusions, since such conclusions are limited to so few studies. Are the search strategies explicitly stated and logical? Yes, given the rules of the study. Are the definitions or diagnostic criteria for the outcome measures appropriate? Yes Are the statistical methods used appropriate? Yes	The inclusion and exclusion criteria were adapted from the original 2008 report and were extensively discussed during the TEP calls. We updated some sections of the study selection criteria based on input from TEP members. After discussions and recommendations from TEP members, we decided to include and focus only on men with clinically localized prostate cancer clinical stage T1 through T3a) in the report. Studies that included a mixed population of patients with T1, T2, T3, or T4 cancers must have provided separate data for T1 through T3a or a subset of those patients. We have now reported that apart from RCTs, well-designed observational studies are needed to provide a useful body of evidence.
TEP Reviewer 5	Methods	The inclusion criteria are justified, but it is not clear why an upper limit of T2 disease was placed. Similarly, the staging errors are not adequately addressed (obviously not an issue in RCT's), but important when trying to potentially identify cohorts of patients who could benefit from treatment. Missing in the analysis, are the statistical analysis plans for the RCT trials considered, as many did not achieve their stated accrual targets (PIVOT being a key example) and the fact that they failed to meet their primary endpoint was not surprising. Table 13 is an example of the diversity of the endpoints being considered, many of which, e.g. biochemical progression, are clinically irrelevant in terms of metastasis free, symptom free, and overall survival. Also, if these trials were considered in contemporary terms, many would NOT have been started.	Thank you. After discussions and recommendations from TEP members, we decided to include and focus only on men with clinically localized prostate cancer (T1 throughT2); since this review the protocol was modified to also include men with stage T3a in the report. Studies that included a mixed population of patients with T1, T2, T3, or T4 cancers must have provided separate data for T1 through T3a or a subset of these patients. We note in the Discussion that failure to achieve stated accrual targets limited the statistical power of RCTs such as PIVOT to detect differences in clinical endpoints, and therefore limited the strength of evidence. We note that both Table 13 (RCTs) and Table 14 (nonRCTs) considered many endpoints that are clinically irrelevant in terms of metastases, symptom-free survival, and overall survival. Based on this premise, we made the decision to report all outcomes in our major findings table but only provide SOE grades for all-cause mortality, overall survival, prostate cancer–specific mortality, progression to metastases, and quality of life.
TEP Reviewer 6	Methods	Very appropriate	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 7	Methods	Little statistical methods required. I believe that lumping PIVOT and SPCG-4 and calling this inconclusive because SPCG-4 had a stat significant benefit and PIVOT did not misses some of the complexity of the studies. PIVOT conducted in the US and primarily involved men with PSA detected tumors. CaP mortality in observation arm very low and more consistent with men currently detected (likely even higher than men currently detected). SPCG-4 conducted in absence of PSA testing, had much higher CaP mortality rates. Any benefit was limited to men age > 65.	Because of the differences in study designs, treatments, patient and tumor characteristics, outcomes reporting, and suggestions from Technical Expert Panel (TEP) members we did not pool the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and Scandinavian Prostate Cancer Group-4 (SPCG-4) studies. We performed only qualitative analysis in this update. We have used the term inconclusive because "Inconclusive" means that the strength of evidence is too weak for us to tell whether there is a difference (favoring one or the other intervention) or not. We have emphasized that a potential explanation for the difference between the two studies is the difference in population characteristics.
Peer Reviewer 1	Results	See General comments.	
Peer Reviewer 2	Results	Well done	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Results	The amount of detail presented is appropriate. Study characteristics are well described. Key messages are explicit and applicable. Figures, tables, and appendices are adequate and descriptive. P 58 (and discussion). The comment that the benefit of surgery for men with low-risk cancers differed between PIVOT and SPCG-4 seems misleading. I don't consider the low-risk PIVOT subjects--the majority of whom were PSA-detected--to be comparable to the low-risk SPCG-4 subjects. Nearly 80% of SPCG-4 subjects had T2 (palpable) tumors vs. only about 45% in PIVOT. P 59. Text and Table 27. PIVOT also looked at PCSM and distant metastases for outcomes. 2 recent observational publications from the Prostate Cancer Outcomes Study to include: 1) Daskivich TJ, et al. Effect of age, tumor risk, and comorbidity on competing risks for survival in a US population-based cohort of men with prostate cancer. Ann Intern Med 2013; 158:709. 2) Hoffman RM, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. J Natl Cancer Inst 2013;105:711. Other observational studies to consider: 1. Sanda MG, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. New Engl J Med 2008; 358:1250. 2. Cooperberg M, et al. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. Cancer 2010;116:5226. Before final publication, you should determine whether Widmark A, et al. have published the survival results for their comparison of EBRT vs. watchful waiting (so far, abstract only): http://www.medscape.com/viewarticle/750994	We have added additional text about the differences in the populations in the SPCG-4 and PIVOT studies. We have added prostate cancer–specific mortality and progression to distant metastases to Table 27 We thank the reviewer for providing the four listed studies for inclusion. Of these four studies, three were included and one was excluded. Included Hoffman et al. 2013[2] Sanda et al. 2008[3] Cooperberg et al. 2010[4] Excluded Daskivich et al. 2013,[5] excluded as a nonRCT with a mixed population and no separate results for patients with T1 through T3a or a subset of those patients. We will continue to be on the lookout for the publication by Widmark et al. as suggested.
TEP Reviewer 1	Results	As the SPCG-4 and PIVOT studies are the only cross-primary-treatment comparisons, their results and ratings of strength of evidence are particularly important. SPCG-4 receives a “low” overall risk of bias score, while PIVOT receives a “medium” risk of bias score (Table 46). The only difference in the data elements appears to be that 85% of enrolled patients were said to have provided data at the time of interest in SPCG-4. Yet median follow-up for SPCG-4 was 12.8 years in the most recent analysis published in 2011. It doesn’t seem possible, then, that 85% of SPCG-4 participants could have contributed results at 15 years. If so, then shouldn’t the SPCG-4 risk of bias be “medium” at 15 years as well?	In our instrument rating scale that was used to assess the risk of bias for individual studies, we made an error in our response to Item 6 on the instrument. You are correct - fewer than 85 percent of the enrolled patients provided data at the followup of 15 years. This has changed the risk of bias from low to medium.
TEP Reviewer 2	Results	See General comments section.	

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Results	The detail in the results section is appropriate. The tables are quite clear, albeit somewhat too plentiful to follow! Page 14 – What is the reference for the method to determine the risk of bias of a given study? Can it be referenced in the text (even if it is only a reference to the previous report) as the authors do for strength of evidence in the subsequent section? Page 15 – Did lowering the evidence grade by one level as described here actually affect any of the outcomes listed in the report? If it never did, this should be described as a strength. If it did change the outcome of the review, it should be highlighted. Page 18 – It seems that a huge number of studies were excluded in order to arrive at the best evidence. While I agree that it is important to perform an analysis of only the best, I think there would be some value to analyzing some of the other studies to see whether there is any particularly important information to be found there. For instance, the 12 RCTs with <100 patients per treatment arm might contain useful information which can be weighted less to reflect the small numbers of patients, without excluding them altogether. Page 36 – Clearly the non-randomized comparative studies all have some degree of bias in their reported outcomes, but, clearly, these studies are not all created equal. Can this review either assess or simply document the measures used to account for bias? – instrumental variables, propensity score matching, multivariable adjustment, stratification, etc. Otherwise, the review makes it seem as though they are all equivalent (and not useful). It might be helpful to summarize early on any substantive differences in findings between the current report and the 2008 report.	Thank you. Pg. 14 We cited the EPC Methods guidance for the assessment of individual study risk of bias: "Assessing the risk of bias of individual studies when comparing medical interventions" in the "Methods Guide."[6] Pg. 15 It did not affect any of the outcomes listed in the strength of evidence grade table. Pg. 18 RCTs were not excluded based on number of subjects enrolled. These studies were excluded for other reasons including: dose escalation study;[7,8] no outcome of interest;[9-13] no comparison of interest;[14-17] biochemically relapsed prostate cancer,[18] immediate surgery vs. delayed surgery[19]; trial was abruptly ended;[20] men had a past history of Transurethral resection of the prostate done already.[21] If needed, we can send a table summarizing the reasons for excluding these studies. Pg. 36 We already included in our study selection criteria (see Table 6 in the report) that "For any nonrandomized comparative studies, we included only those that used an analytic method to address selection bias, such as intentional baseline matching on multiple characteristics, propensity scoring, or other analytic approach. The treatments being compared must have been administered during the same time period, so that any observed difference between outcomes were not attributable to differential time frames." In addition, we have now rated studies that used instrumental variable analysis as superior to studies that used other statistical methods to adjust for confounders. We have now added findings from the current report and 2008 report.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	Results	Are figures, tables and appendices adequate and descriptive? Yes Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? Several large multi-institutional Phase III trials for the treatment of prostate cancer involving radiation therapy are excluded. As a result the conclusions are based only upon 3 randomized trials with RT (Jones et al NEJM, D'Amico et al JAMA, and Widmark et al Lancet Oncology). There are at least 7 trials that evaluated RT plus or minus ADT RTOG 8531 RTOG 8610 EORTC Bolla 1 trial D'Amico Study (noted) RTOG 9408 (noted) TROG 9601 Casodex 150 trial In addition, a number of trials tested the duration/timing of ADT RTOG 9413 EORTC Bolla #2 trial Canadian trial of 3 vs. 8 months TROG 9601 Two published trials evaluated ADT plus or minus ADT Widmark trial (as noted) NCIC trial Finally, 3 trials assessed the role of RT after RP with high risk pathalogic features SWOG EORTC German As a result this report seems to indicate that the role of radiation is evaluated with a very small number of randomized trials when instead it has been evaluated with a very large number of phase 3 trials that are not indicated. The most recent relevant publications include: 1. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Colombel M, van de Beek C, Verhagen P, van den Bergh A, Sternberg C, Gasser T, van Tienhoven G, Scalliet P, Haustermans K, Collette L; European Organisation for Research and Treatment ofCancer, Radiation Oncology and Genito-Urinary Groups. 2. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Billiet I, Torecilla JL, Pfeffer R, Cutajar CL, Van der Kwast T, Collette L. Lancet Oncol. 2010 Nov;11(11):1066-73. doi: 10.1016/S1470-2045(10)70223-0. Epub 2010 Oct 7.	As stated above, the report focused only on men with clinically localized prostate cancer (T1 through T3a). Studies that included a mixed population of patients with T1, T2, T3, and T4 cancers must have provided separate data for T1 through T3a or a subset of those patients. We have reviewed all the studies suggested by the reviewer and found they did not meet the inclusion criteria for the report. Below are the reasons for excluding the following studies: Bolla et al. 2012;[22] Bolla et al. 2010;[23] Bolla et al. 2009;[24] Warde et al. 2011;[25] and Horwitz et al. 2008.[26]—all these studies included men with more than 15% T3 and/or T4 populations and none of them provided separate results for men with T1 and/or T2 or T3a, which is the focus of the report. These studies are all outside the scope of the report. Future reports that address men with T3b and T4 may include these studies. We acknowledge that patients with clinically localized prostate cancer undergoing radiation therapy as primary therapy are likely to be understaged, and further, that a fair comparison of radiation with or without androgen deprivation to RP might best be done in a population with nonmetastatic disease. However, that was not the population specified in our review protocol. Until staging systems reframe prostate cancer staging in this way, we believe that evaluation of this comparison will be difficult. At present there is a need to define which patients are most appropriate for watchful waiting, active surveillance, or therapies such as surgery, radiation. or hormonal therapy.

Commentator & Affiliation	Section	Comment	Response
		(continued) 3. Duration of androgen suppression in the treatment of prostate cancer. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, Gez E, Kil P, Akdas A, Soete G, Kariakine O, van der Steen-Banasik EM, Musat E, Piérart M, Mauer ME, Collette L; EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. N Engl J Med. 2009 Jun 11;360(24):2516-27. doi: 10.1056/NEJMoa0810095. 4. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, Gospodarowicz M, Sanders K, Kostashuk E, Swanson G, Barber J, Hiltz A, Parmar MK, Sathya J, Anderson J, Hayter C, Hetherington J, Sydes MR, Parulekar W; NCIC CTG PR.3/MRC UK PR07 investigators. Lancet. 2011 Dec 17;378(9809):2104-11. doi: 10.1016/S0140-6736(11)61095-7. Epub 2011 Nov 2. 5. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advancedprostate cancer. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, Venkatesan V, Lawton CA, Rosenthal SA, Sandler HM, Shipley WU. J Clin Oncol. 2008 May 20;26(15):2497-504. doi: 10.1200/JCO.2007.14.9021. Epub 2008 Apr 14	
TEP Reviewer 5	Results	The results are indeed comprehensive and essentially show that the level of evidence for treatment very limited. In short, similar to the 2008 results. A key issue is how can the results of the present analysis be used to insure that future trials ask clinically relevant questions for which answers can be obtained. Consider the incredible waste of resources this effort summarizes, which simply has to end. This Reviewer would be very interested in how the unique expertise of this group can be channeled to guide the research community on what to avoid when designing future trials. Given the morbidities that can result from overtreatment, and the economic impact, it is essential that this cycle of “doing trials because we can” simply has to end.	Thank you. We have included in our Research Gaps section some of our suggestions that can be implemented to guide future study investigators embarking on new trials. Some of our suggestions include (1) Information on how better-quality observational studies can be conducted to adjust for baseline differences between study groups and (2) the need for better prognostic surrogate markers to predict the risk of recurrence among men with clinically localized prostate cancer.
TEP Reviewer 6	Results	Nice balance of data. Good evidence tables	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 7	Results	1) PIVOT vs. SPCG-4: likely little difference in management approaches in the observation arm. I recommend minimizing discussion here...both designed as pragmatic trials to minimize definitive intervention or treatments for asymptomatic disease-given this report is for US and current practice perhaps increase emphasis on US trials and those conducted in PSA era 2) Do not believe data support statement that evidence indicates that outcomes favor RP over observation (especially in men with PSA detected disease) 3) Additional comment on outcomes among men currently detected by PSA testing would indicate that risk of cancer mortality through 12 years with observation is low and unlikely to be reduced by early intervention (in PIVOT < 10% and among men with "definite death due to prostate cancer" difference between RP and WW were < 1%) 4) ARD in PIVOT for CaP and all-cause mortality were < 3% and NS (not a trend as noted) 5) Outcomes according to Comorbidity and Gleason scores reported in PIVOT and not provided here 6) Data do not support statement that outcomes are improved with "newer" technologies as authors report. Several papers have addressed this and especially for men with low PSA/low risk disease outcomes NOT superior to WW and are more expensive and increase harms 7) Scandinavian trial of WW vs. EBRT reported at meeting and abstract-agree not published but authors could comment (results NS for mortality) 8) Ongoing UK trial of RP vs. EBRT vs. AS (ProtecT) could be mentioned 9) Additional data on periprocedure harms could be emphasized (esp for RP) 10) mets not described in ES 11) A greater discussion/display of the absolute findings would be of value in the ES 12) Given the relatively few of RCTs I believe it might be more useful to display event rates and ARD differences and perhaps minimize space used for nonRCT.	1) Based on our review, we believe that there are enough differences in the management approach in the observation arms of PIVOT and SPCG-4 to be worth noting in the discussion. 2) Based on the data reported in the SPCG-4 trial, the effect size for both all-cause mortality and prostate cancer–specific mortality favored men who underwent radical prostatectomy (RP) compared with observation. We understand that this may apply only to men without PSA-detected disease, and have noted the differences in patient populations in our Discussion section. Regardless, the strength of evidence (SOE) was graded as insufficient for both outcome measures. 3). As mentioned, we have noted the specific characteristics of patients in PIVOT and how this may have affected outcomes, but in any case the evidence was insufficient for a conclusion. 4). We have removed the word “trend” and simply noted that this was a nonsignificant difference. 5) We have included Charlson score along with other subgroups such as race, age, and self-reported performance score in Table C of the Executive Summary. We discussed all subgroups in our Results section and also provided the SOE grading for each subgroup in Table 24 of the report. 6) We have deleted this suggestion and noted under Limitations that newer technologies have not been adequately addressed in RCTs. 7) We thank the reviewer for providing information reporting that results were nonspecific for mortality in the Scandinavian trial of WW vs. EBRT that was reported in a meeting abstract. However, we do not comment on meeting abstracts or unpublished data in the report. 8) The ProtecT study described in Table 69 in Appendix H of the report has now been included in our discussion as suggested.

Commentator & Affiliation	Section	Comment	Response
			9) We have added the following information to our Discussion section: "Urinary incontinence, bowel incontinence, and erectile dysfunction were mostly reported among men who underwent RP. Conversely, genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction were reported among men who received radiation therapy." 10, 11, 12) We have now added data on metastases, more data on event rates and absolute risk difference (when reported by study investigators) to the RCT data summary tables in the Executive Summary. We have also minimized the amount of data on nonrandomized studies in the Executive Summary.
Peer Reviewer 1	Discussion and Conclusion	See General comments.	
Peer Reviewer 2	Discussion and Conclusion	one meta-analysis of 6 vs 3 or 4 mos of HT for men treated with EBRT is worth considering b/c it suggests for men with Gleason 7 PC that 6 is better than 3 or 4 mos.	We considered studies which compared variants of the same treatment as out of scope for this report.
Peer Reviewer 3	Discussion and Conclusion	The review presents an understandably bleak view of the literature. The few RCT report on outmoded diagnostic strategies and treatments. Observational studies have a high risk for being biased. However, concluding that we need rigorously designed RCT seems disingenuous. RCT have had challenges achieving target enrollments and been unable to compare different modalities with the exception of surgery vs. watchful waiting. This suggests comparative effectiveness research to guide treatment decisions will likely require well-designed observational studies. I'd like to see the review address strategies for ensuring that observational studies appropriately attempt to minimize bias, e.g., prospective population-based cohorts, use of propensity-score or instrumental variables, use of validated quality of life measures. I also think that there is substantial evidence that men with low-risk screen-detected cancers are not likely to benefit from active treatments--suggesting that RCT for such patients should focus on various strategies of active surveillance. RCT comparing active treatments should be conducted just in men with higher-risk cancers. The review could also note the need for better prognostic surrogate markers--biochemical progression has limited discriminant value.	Thank you for your feedback. We have now revised the future research section in an attempt to provide equal emphasis for RCTs and nonRCTs that are appropriately designed to minimize the risk of selection bias. We believe that information from both study designs may be useful to guide future clinical decision-making. We have also added to the Research Gaps section the need for better prognostic surrogate markers to predict the risk of recurrence among men with clinically localized prostate cancer and among men that are being managed by active surveillance. We have now added that future RCTs should place more emphasis on different approaches of treating patients who have clinically localized prostate cancer (particularly low-risk patients) using active surveillance. We agree that this is one of the areas where future RCTs might provide the most benefit.
TEP Reviewer 1	Discussion and Conclusion	Yes, clearly stated. The list of ongoing trials is valuable.	Thank you. We have also updated this list based on new searches conducted in March 2014.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	Discussion and Conclusion	See General comments section.	
TEP Reviewer 3	Discussion and Conclusion	Yes, the implications for policy makers are clear. Future research is addressed Page 78 and 82 – It might be useful to call for the inclusion of more African American patients into randomized trials of prostate cancer therapy. Page 83 -- Also, the lack of demonstrated efficacy at 12 years between treatment methods is noted often throughout the text as well as the demonstrated benefit at 15 years. This should be no surprise given the protracted course of most prostate cancers. This should be noted so that the observation does not appear to discredit the 15 year findings, but rather add credence to them.	Thank you. Pg. 78 and 82 We have added a suggestion to the Research Gaps section in the report about the need for more participation of African Americans in future studies. Pg. 83 We agree and have noted this in the Discussion.
TEP Reviewer 4	Discussion and Conclusion	Are the implications of the major findings clearly stated? Yes Are the limitations of the review/studies described adequately? Yes In the discussion, did the investigators omit any important literature? Yes Is the future research section clear and easily translated into new research? Yes	Thank you.
TEP Reviewer 5	Discussion and Conclusion	Continuing the theme above, it is not enough to outline the questions, which based on the results of the analysis have not changed. “Suggestive evidence” of benefit is inadequate and insufficient. The central issue is are these questions in fact answerable, and if so how. This is not well addressed. An additional suggestion would be to detail some of the systematic methodologic errors in trial design as a check list for Investigators and Reviewers so that the chance of answering a question is increased.	We acknowledge that it will be difficult to find a definitive answer to these questions. The best that can be done is for investigators to continue performing long-term followup studies that are well designed and completed as intended. The RCTs should use standardized or validated methods to determine patient outcomes and have adequate power to detect significant treatment effect. Better-quality observational studies (e.g., cancer registries and large, prospective, population-based cohort studies, use of instrumental variables, use of validated quality-of-life measures) may also provide useful evidence, particularly in cases in which large differences in outcomes might exist.
TEP Reviewer 6	Discussion and Conclusion	The only question is whether the report should stress that there should be a national dialogue to attempt to re-try a true RCT for 2-3 treatments for localized prostate cancer. We’ve tried, on 3 occasions, and failed, generally because physicians won’t participate.	We believe that it is beyond the purview of this report to call for a national dialogue on this issue.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 7	Discussion and Conclusion	Given the uncertainty and concern re: ROB for nonRCTs and 2 AHRQ funded CER noting limitations of nonRCTs do not believe that emphasis should be placed on future research that includes nonRCT. Agree that current RCTs were initiated many years ago and there has been evolution in diagnosis and treatment. Given detection of smaller volume tumors and histologic upgrading the long term outcomes of detected CaP in men managed with observation (or not detected) are likely much better than when these studies initiated and the risk of overdiagnosis and overtreatment greater (this includes the harms of AS with biopsies and infection/hospitalziation). Any benefit of early interventino likely to be smaller in absolute terms and require longer to accrue...thus any harms would weigh even more importantly...this should be discussed. Given low CaP mortality in men in PIVOT (early PSA era) the likelihood of any greater than a small mortality benefit for early intervetnion esp in men with low PSA /low risk disease is very low-and it causes harm and costs more (mutliple decision and cost analyses have demonstrated this)....this could be discussed at greater length. A major research need is 1) avoiding overdiagnosis and overtreatment 2) implement and disseminate these findings to enhance use of observation rather than early inteventions in men with PSA detected, esp low PSA/low risk disease...or reducing costly use of expensive interventions (robot, proton, IMRT etc) esp in men wiht low PSA/low risk disease...3) future RCTs. of early intervenion should target higher PSA/higher risk disease as CER or vs. AS (given that the benefits in this group are 10% or less through 12 years). 4) Consideration of multiparametric MRI (mpMRI) as a tool to enhance use of observation or AS 5) or consideration of the need for high quality studies limitation in approval of interventions before the wide spread use of interventions of high costs and harms with little to no evidence of benefit.	We have revised the future research section in an attempt to provide equal emphasis for RCTs and nonRCTs that are appropriately designed to minimize the risk of selection bias. We believe that information from both study designs may be useful to guide future clinical decisionmaking. We have also added to our discussion section as suggested to report low rates of prostate cancer–specific mortality in men in PIVOT (early PSA era) and the low likelihood of any more than a small mortality benefit for early intervention, especially in men with low PSA/low-risk disease, and that early intervention causes harms. We did not discuss costs because cost analyses issues are outside the scope of the report. Finally, we thank the reviewer for all the suggestions and have adapted and included the major research needs as listed by the reviewer in our Research Gaps section.
Peer Reviewer 1	Clarity and Usability	See General comments.	
Peer Reviewer 2	Clarity and usability	Well presented and well qualified.	Thank you.
Peer Reviewer 3	Clarity and Usability	The report is well structured and organized with clearly presented main points. I think the report could go further in informing policy and practice decisions by emphasizing how new technologies (e.g. robotic surgery, stereotactic radiotherapy, proton beam therapy) are being widely adopted and then reimbursed at substantially higher rates than older modalities--despite the absence of convincing evidence for greater efficacy. This message should be clearly spelled out for patients considering treatment options and for the government and commercial entities whose financial support for these new technologies is driving up health care costs without a clear commensurate increase in health care quality.	Thank you. We have noted that newer technologies have not been adequately evaluated in well-designed studies in the Discussion, and suggested that future studies are needed for these interventions.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 1	Clarity and Usability	Yes.	Thank you.
TEP Reviewer 2	Clarity and Usability	See General comments section.	
TEP Reviewer 3	Clarity and Usability	Yes, the organization of the report, tables and executive summary is excellent	Thank you.
TEP Reviewer 4	Clarity and Usability	Is the report well structured and organized? Yes Are the main points clearly presented? Yes Can the conclusions be used to inform policy and/or practice decisions? No	Thank you. Perhaps policy and practice decisions will be better informed once it is possible to better define those subpopulations likely to benefit from radiation therapy, surgery, or hormonal therapy.
TEP Reviewer 5	Clarity and Usability	The report is well organized and exhausting to read. The points are clearly presented but the analysis can be improved.	Thank you. We have reworded our entire qualitative analysis throughout the report for better clarity.
TEP Reviewer 6	Clarity and Usability	Useful. Nice executive summary	Thank you.
TEP Reviewer 7	Clarity and Usability	See Discussion and Conclusion Section	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General	This report addresses a clinically significant issue – management of non – metastatic prostate cancer, a significant public health concern given it incidence, concerns about over – detection and – treatment, the costs of care (financial, physical and psychological) and inconsistent evidence of the benefits of one treatment (or non – treatment in some cases) approach as compared to another. It is a significant undertaking - very well written, excellent methods which very well described. The summary and limitations sections are excellent and inclusive. Despite the acknowledged limitations of the research to date, the report is clear and will be of considerable value to a wide variety of readers. I have the following comments. 1. Page – 12, Line 28 – what constitutes a "normal" PSA is, in itself. A subject of much debate (i.e. uniform cut point, age stratified testing, etc.) 2. For both the Executive summary and full report it might be of value to note that the TNM staging system is likely to be revised shortly. In addition, the risk assessment scheme described, although commonly used, has significant limitations is assessing those in the intermediate and high – risk groups. It would be worthwhile to describe other risk assessment schemes that have been developed, validated across populations and associate with both overall – and – cause specific survival (Eur Urol. 2013 Apr 8. doi:pii: S0302-2838(13)00352-7. 10.1016/j.eururo.2013.03.058. BJU Int. 2013 Mar;111(3):427-36. doi: 10.1111/j.1464-410X.2012.11400.x. Epub 2012 Aug 9. Review. Urol Int. 2012;89(1):45-51. D. Radiother Oncol. 2011 Dec;101(3):513-20. doi: 10.1016/j.radonc.2011.05.080. Epub 2011 Jun 22.PMID:21703711, etc). it would also be advisable to highlight that such risk assessment tools are likely to be improved with the use of biomarkers (J Clin Oncol. 2013 Apr 10;31(11):1428-34. doi: 10.1200/JCO.2012.46.4396. Epub 2013 Mar 4.PMID:23460710) 3. Both sections say AS should be offered to men with "low risk" disease. However, it is becoming increasingly clear that some in the "intermediate risk" category may be candidates for such and approach (pointing to the limitations of the risk assessment scheme described). Indeed some of the trials you describe support the notion that treatment of some men with intermediate risk disease may have little to no impact on prostate cancer specific survival compared to observation (Abdollah et al) 4. I am not sure why men with T3 disease were excluded form analysis 5. Should freedom form hormonal therapy, known to be associated with significant side effects, be included as an outcome or at least mentioned as something to be considered, in the absence of well documented literature on this event (II Analytic, Table 6)	We thank the reviewer for all suggestions. 1. We agree that the cutpoint for "normal" PSA is debatable and have now noted this in the Background. 2. We have also updated the Background section throughout the entire report with more information on other risk assessments described in the report. We have added a statement on The Cancer of the Prostate Risk Assessment (CAPRA) with all appropriate citations suggested by reviewer. We have also added a statement about biomarkers. 3. We have added a statement to Research Gaps indicating future trials of AS are warranted in intermediate-risk patients. 4. The report focuses only on T1 through T3a cancers. We had numerous discussions with TEP members and decided to keep the population consistent with the original report (T1 and/or T2 patients). T3a has since been added based on the recent NCCN guideline.[27] The population with >T3a locally advanced or regionally advanced but nonmetastatic disease is a different population. We recognize that some patients thought to have T2 disease are found to have more advanced disease at surgery. 5. We did not include this as an outcome because we already included adverse events of any kind, so any increase in adverse events with hormonal therapy should appear under adverse events. Freedom from hormonal therapy does not tell us how many patients would have experienced side effects if they had been prescribed or continued this therapy. 6. As suggested by the reviewer, we have cited the study by Etzioni et al. 2013,[1] to point out that some experts believe that the U.S. Preventive Services Task Force (USPSTF) report does not give sufficient consideration to the limitations of screening trials on which their recommendations were based.

Commentator & Affiliation	Section	Comment	Response
		(continued) 6. I think it would be important to point out that many feel that the USPTF's report is misleading on several points. I think that if you are going to give estimates based on the report, it would be important to point out that others think they have underestimated the effects of PSA testing (Med Care. 2013 Apr;51(4):295-300. doi: 10.1097/MLR.0b013e31827da979) 7. With regard to KQ 3, there is a growing concern that financial incentives (a provider characteristic) drive treatment selection and costs (http://www.gao.gov/assets/660/656026.pdf). Given the diverse readership of this report, should this be referenced at least somewhere in the document?	(continued) 7. Based on the suggestion by the reviewer, for Key Question 3, we have added a statement about the Government Accountability Office report that notes the financial incentives issue.[28]
Peer Reviewer 2	General	The report is clinically meaningful but highlights the limited amount of level 1 evidence in this area. (1) Re: RCT's of RP vs WW - it is important to note that the subgroup analyses of PIVOT that suggest benefit in men with PSA > 10 or int risk dz is c/w the Swedish study where most of their cohort comprised such men. Taking together this may increase the SOE in this subgroup. (2) When seeing the the HR for PCSM are similar between the PIVOT and Swedish study but that the HR for ACM was higher in PIVOT then the Swedish study suggests that PC death in the PIVOT study was diluted by deaths from other causes or competing risks which speaks to the underlying health of the men in the 2 RCT's being different and questioning whether the PIVOT data can apply to a healthy cohort - this is detailed in a report by Aizer et al in BJU Int. 2013 Mar 8. (3) Re: the RCT's of EBRT +/- HT, it appears that int risk appears to benefit from 4 to 6 mos of HT but these studies could not address the issue of 3 + 4 vs 4 + 3 or the impact of pecent + biopsies > 50% or tertiary grade 5 on the study endpoints where longer term HT may be needed and this should be mentioned.	Thank you. 1) We have noted in the Discussion that there is overlap in this subgroup, although we believe that there is still too much uncertainty to warrant increasing the SOE. 2). We have noted in the Discussion that the underlying health of men in SPCG-4 and PIVOT may have been different. The Aizer et al. 2013 study compared patients treated with curative versus non-curative treatments which were broad categories not considered in this report. 3). We have noted in the Discussion that for higher risk patients, longer term HT may be needed to detect a benefit,
Peer Reviewer 3	General	The report is clinically meaningful, with well-described target populations and target audiences. The key questions, which were previously used in the 2008 report, remain appropriate.	Thank you.
TEP Reviewer 1	General	Yes, I think the report overall is thorough and adequately defines the limits of the available evidence. The target population and audience are defined appropriately. The key questions are the right ones.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	General	General Comments: Currently written, this guideline adds no value to the current literature and if published will significantly harm scientific progress to date by significantly clouding the outcomes. The key questions asked are do not focus on the clinically important questions, the literature search has failed to identify key articles and the summary of articles doesn't provide any clarity (despite multiple RCTs all showing similar direction and magnitude of benefit). This review has probably failed in that tried to address the entire spectrum of prostate cancer management when really low, intermediate, high-risk and metastatic disease are all separate clinical entities. Unfortunately, I cannot endorse the guideline as currently written. My main criticisms/concerns are: the key questions are too broad and therefore not clinical applicable. For example, KQ1 is: "What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?" Very low, low, intermediate and high-risk localized prostate cancer are considered separate clinicopathologic entities yet the outcomes for all these patients for all the treatments of interest are considered together. To illustrate my point, the 5-year biochemical disease-free survivals range from 34 – 99% depending on the initial management approach and risk. Suggested key questions might be: is there evidence of improved outcomes with radical treatment of very-low or low risk prostate cancer versus conservative strategies (active surveillance or watchful waiting – these could be considered separate if desired) What are the comparative risks and benefits for intermediate-risk prostate cancer (rP vs RALRP vs brachy vs brachy/EBRT vs Cryo vs HIFU etc). Care will have to be taken to ensure the same population is in both treatment cohorts (ie., patients that could have surgery or brachy in one example). Pairwise comparisons should be done for each of the interventions (unless the study has more than two interventions, although there exist very few of these that would meet your search criteria to my knowledge) For high risk prostate cancer, what are the comparative risk / benefits of: i) EBRT/ADT over ADT alone; ii) EBRT vs long-term ADT; iii) EBRT + short-term ADT vs EBRT + long-term ADT; iv) rP +/- EBRT +/- ADT vs EBRT + ADT; v) whole pelvis RT + ADT vs prostate only RT + ADT; vi) EBRT + ADT vs EBRT + brachy + ADT; vii) rP + observation vs rP + adjuvant RT; viii) salvage RT vs salvage RT +/- ADT; ix) rP vs neoadj chemoADT vs rP alone	We appreciate the new key questions suggested by the reviewer and the entire feedback. While the report is not a guideline, it could be used by guideline developers. This update examined the same 4 key questions as the original 2008 report on the comparative effectiveness of treatments for clinically localized prostate cancer. This update summarizes the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. Key question 4 attempted to address the issue of whether differences in tumor risk categories affected clinical outcomes after various interventions. We included any comparators that were described in any studies that met our inclusion criteria. This included brachytherapy, as well as a variety of other treatment modalities. The strength of evidence grading was reported only for patient-oriented outcomes. For intermediate outcomes such as biochemical disease free-survival, we reported in Results section only the data from the original studies that met our inclusion criteria. In regard to the comment that other high quality guidelines were not included in the search strategy, we note that this report is not a guideline. Our criteria for evaluating evidence required data from published clinical studies. Guidelines are based on a review of available evidence combined with expert opinion. As such we do not consider them a source of original data.

Commentator & Affiliation	Section	Comment	Response
	General	(continued) Many RCTs have been performed (and published) which have shown that higher biological dose equivalents improve biochemical disease-free survival. Yet no acknowledgement of this has been built into the document (that I saw). For example RT should include only “modern” RT doses of 76 Gy or greater (EQD2). Large comparative studies of brachy vs EBRT have generally shown better tumor outcomes and similar/lower toxicities. Why isn’t brachy the (RT) comparator? There doesn’t appear to be other (high quality) guidelines included in the search strategy. This is standard in most other guideline efforts (ASCO, CCO, Cochrane) I’m not sure whether my feedback is even helpful at this stage. It seems that this project has gone too far “off the tracks” to quickly salvage. I’m happy to help correct the course if desired.	
TEP Reviewer 3	General	The key questions are appropriate and explicitly stated. The report is probably more relevant to policy makers and less to clinical decision-makers because it leaves out a great number of observational studies and clinical trials which are often used as the basis for decision-making in the absence of level I evidence.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	General	The report is well written and conforms to the rules it has laid out for itself in terms of literature review, management of bias, interpretation of results and answering of the 4 questions. Yet the report rings hollow given its conclusion that future RCT's remain necessary to answer the question of treatment decision for localized prostate cancer. The report sets up a null hypothesis when reading its intent now or in the future to direct decision making for localized prostate cancer. It rejects and/or down plays the results of RCT's as 'outdated' given the changes in the diagnosis and natural history of prostate cancer in the PSA era, as well as changes in surgical and radiation technology. The report further suggests that additional trials are necessary to assess the efficacy and safety of emerging technologies, yet to be followed by RCT's comparing different treatments. Understanding the 'rules' necessary to present legitimate conclusions, there will always be issues with prostate cancer that may be unique and which will always confound a study such as this. First, the natural history of this disease and the need for protracted follow-up will have trials cross over new treatment technologies, discovery algorithm's and pathologic or laboratory tests. Second, the fact that localized prostate cancer rarely has significant impact on patient population mortality, the power to address mortality (a key question in treatment decision) will always be limited, and lastly, the current political environment in the US and abroad regarding therapy has made and will make participation in appropriate RCT's impossible to achieve. Given these issues linked to a report that fails to provide guidance to the medical community, its applicability is not clear and it offers little value to the end-user. I fear that the report will be used as evidence that comparative effectiveness research is a scam and that its applicability to the 'real world' is distant at best. And keep in mind I am a believer in this effort. And while the conclusions are true that there remains little evidence to help in decision making for men with localized prostate cancer, the political atmosphere around this disease coupled with its high incidence, strong advocacy base, corporate investments in technology and the overall-cost to society of its treatment, I am concerned that this report will be distorted as a governmental boondoggle. Given that the answers to each of the four questions fail to assist with real-life decisions in the clinic, the AHRQ may want to address its 'rules' for this evaluation and reconsider a different approach of CER for this disease.	Thank you. As stated above, the inclusion and exclusion criteria were adapted from the original 2008 report and were extensively discussed during the TEP calls. We updated some sections of the study selection criteria based on input from TEP members. The report focused only on men with clinically localized prostate cancer (T1 through T3a). Studies that included a mixed population of patients with T1, T2, T3, or T4 cancers must have provided separate data for T1 through T3a or a subset of those patients. We have now reported that apart from RCTs, better-quality observational studies are needed to provide a useful body of evidence. Based on suggestions from other external reviewers, we have added new information addressing many of the issues to the Applicability section of the report.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	General	The report catalogs the results of trials reporting outcomes in localized prostate cancer defined as clinical T2 or less. The questions that are defined and addressed are of direct clinical relevance to patients considering their treatment options and Physicians who are making treatment recommendations. A weakness is the critical analysis of the results and a statement regarding overall failure of the research community to answer them despite the commitment and utilization of huge patient and financial resources.	Thank you. As noted above, we have reworded our entire qualitative analysis throughout the report for better clarity. Additionally, we have updated our Implications for Clinical and Policy Decisionmaking section to discuss some of these issues.
TEP Reviewer 6	General	Report is clear, questions are clear. Conclusions are appropriate and useful, given the lack of information upon which to make recommendations	Thank you.
TEP Reviewer 7	General	Generally clearly written with appropriate focus on PICO of interest. I believe there are some misinterpretations of findings as noted below as well as recommendations for future research needs	Thank you. The specific concerns about interpretation of findings and the research gaps were addressed above.
Public Review 1: The Proton Therapy Consortium The National Association for Proton Therapy The Particle Therapy Co-Operative Group—North America The Brotherhood of the Balloon	Executive Summary	Quality of report: Good	We thank the reviewer for finding the time to review and make suggestions on the report.

Commentator & Affiliation	Section	Comment	Response
	General	Thank you for the opportunity to submit comments on the Draft Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Comparative Effectiveness Review (the "Draft Report"). In light of the letter we submitted to the Scientific Resource Center on May 28th, 2013 summarizing recent proton beam therapy (PBT) evidence (the "PBT Survey")(Attachment 1), we were disappointed to see that the Draft Report did not (i) incorporate the promising PBT evidenced we included in the PBT Survey, or (ii) acknowledge the methodological flaws of the Sheets et. al. study. Taken together, the evidence summarized in the PBT Survey demonstrates that proton beam therapy: Provides a safe, effective and minimally toxic treatment for certain prostate cancer patients, Achieves the smallest changes in quality of life compared to either IMRT or 3DCRT,Achieves quality of life scores similar to men who did not carry a diagnosis of prostate cancer, Reduces the risk of a second malignant neoplasms (SMN) in prostate patients compared with contemporary IMRT, and Does not appear to increase either the risk of hip fracture or hip pain in the first four years of follow-up compared to expected rates in an untreated population of men. DM_US 41582473-1.092385.0011 Given the importance of the PBT Survey evidence to patients, physicians, policymakers and other stakeholders, we respectfully request that you reconsider the evidence selection criteria for the final report to include this PBT Survey evidence or, at a minimum, appropriately acknowledge the PBT Survey evidence, promise of the findings and on-going development of the body of published proton beam therapy research.	We thank the reviewer for the comments. All the included studies in the report were based on selection criteria developed after various discussions with TEP members. We provided a list of various treatment options that are used for the management of clinically localized prostate cancer in the report. We also included a list of 8 ongoing clinical trials. Studies that did not meet the inclusion criteria were excluded and reasons are provided below. The Sheets et al. study was included because it met the inclusion criteria for the report and we presented the results as reported by the study investigators. In our Research Gaps we already had highlighted the fact that the included nonrandomized comparative studies were mostly rated as having a high risk of bias based on the methodological criterion presented in our report. We therefore see no need to single out the Sheets et al. study to report specific methodological flaws because the majority of observational studies were deemed to be at high risk of bias. Furthermore, our analysis deemed the evidence for all treatment comparisons in the Sheets et al. study as insufficient to allow conclusions about the comparative effectiveness of these treatments. Additionally, we also suggested that future high-quality studies were preferred to provide better quality of evidence. We thank the reviewer for providing us with a list of suggested studies for consideration. Below we provide the reason for excluding almost all the studies that were sent in the attachment. Apart from the study by Sheets et al. 2012,29 none of these studies met the inclusion criteria. Most were either case series, nonrandomized comparative studies with number of patients fewer than 500, included a mixed population of patients and did not provide any separate results for patients with T1 through T3a, did not have any comparison of interest, or were narrative reviews.

Commentator & Affiliation	Section	Comment	Response
	General	With respect to the *Sheets et. al.* study, this study suffered from a number of critical methodological flaws. Notably, a significant number of proton patients *actually received 3DCRT with photons* to a large whole pelvic field in addition to protons. The use of colonoscopy as a surrogate endpoint also flawed the analysis, particularly when routine *prospective toxicity tracking with colonoscopy was used in connection with PBT* but was not likely used in the community setting for other therapies. Moreover, no data on actual radiation field sizes or doses were available (but the study's era strongly suggests that the proton doses were substantially higher). One must also consider that differences may be more pronounced with longer follow-up as late toxicities may not completely manifest for 2-6 years in some cases. In light of these flaws, a diverse group of clinical leaders that offer multiple modalities of treatment to patients (and included the clinical team that treated the vast majority of the patients in proton arm of the *Sheets et. al.* study) submitted critical analyses to JAMA (letters were submitted by internationally recognized cancer care leaders from The Mayo Clinic, The University of Florida, The Loma Linda University Medical Center and The University of Pennsylvania). *See Letters, Radiation Therapy Modalities for Prostate Cancer, Nancy P. Mendenhall, MD; Steven Schild, MD; Jerry Slater, MD: JAMA. 2012;308(5):450. See Also, Letters, Radiation Therapy Modalities for Prostate Cancer, Curtiland Deville, MD; Edgar Ben-Josef, MD; Neha Vapiwala,MD: JAMA. 2012;308(5):450.* ***Given the serious methodological flaws of the Sheets et. al. study, we respectfully request that the final report address these flaws or, at a minimum, acknowledge that a number of leading cancer centers that offer multiple treatment modalities for prostate cancer patients have questioned the methodology and validity of the study's conclusions.*** Ultimately, patients and physicians have a number of options when approaching prostate cancer and we believe that all options, including active treatment options, should be available through an informed decision making process. Thank you again for the opportunity to provide these comments. We look forward to the continued cooperation and dialogue between our organizations and the proton community's world-renowned cancer center leaders.	**2013** Henderson et al. 2013[30] (case series, N=171) Valery et al. 2013[31] (case series, N=382) Gray et al. 2013[32] (nonRCT, N=371) Efstathiou et al. 2013[33] (narrative review) and Mouw et al. 2013[34] (narrative review) Mendenhall et al. 2012[35] (case series, N=211) Yu et al. 2013[36] (this nonRCT evaluated a mixed population of patients and did not report exact T stage in its baseline patient characteristics table. We excluded it based on the fact this was a study with a mixed population of prostate cancer patients and did not provide separate results for men with T1 and or T2 prostate cancers) Sheets et al. 2012[29] (this nonRCT has already been included in the report). Lee et al. 2012[37] (study compared men with prostate cancer vs. men who did not carry a diagnosis of prostate cancer) Coen et al. 2012[38] (nonRCT, N=196) **2011** Nihei et al. 2011[39] (case series , N=151) **2010** Talcott et al. 2010[40] (this study compared two different doses). Yoon et al. 2010[41] (study compared 5 patients with prostate cancer vs. 5 patients with head and neck cancer) **2009** Fontenott et al. 2009[42] (case series, N=3) **2008** Vargas et al. 2008[43] (case series, N=10) **Last page of the document** Choi et al. 2011[44] (nonRCT, N=15)

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