Evidence-based Practice Center Systematic Review Protocol

Project Title:

Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer: An Update of a 2008 Comparative Effectiveness Review

I. Background and Objectives for the Systematic Review Update

Prostate Cancer

Prostate cancer is the most common nondermatologic cancer in men.[1,2] American Cancer Society data show that in 2012, an estimated 241,740 men were expected to receive a diagnosis of prostate cancer and 28,170 were expected to die from the disease.[1] Approximately 90 percent of those who receive such a diagnosis have cancer confined to the prostate gland (clinically localized disease). Since 2004, the prostate cancer incidence rate has decreased by 2.7 percent annually among men 65 years of age or older and has remained steady among men younger than age 65.[1] The major risk factors for prostate cancer are advanced age, race, and ethnicity (the highest incidence is in African Americans), and family history.

Many cases of prostate cancer have a protracted course if left untreated. Many men die with prostate cancer, rather than from it.[3] During its early stages, clinically localized prostate cancer is usually asymptomatic.[4] However, as the cancer grows, it may cause urinary problems, such as blood in the urine, pain or a burning sensation during urination, a weak urine stream, inability to urinate, and frequent urination, especially at night. These presenting symptoms along with a physical examination, prostate-specific antigen (PSA) levels, and biopsy may be used to evaluate patients for the presence of prostate cancer.

The practice of evaluating healthy men with no prostate symptoms for prostate cancer is controversial. The PSA test is used to measure blood levels of PSA, a protein produced by the prostate gland.[4] Elevated PSA levels may indicate prostate cancer, but elevations are also seen in conditions such as benign prostatic hyperplasia and prostatitis. In contrast, some patients with prostate cancer do not have elevated levels of PSA.[5] In recent years, more frequent use of PSA testing has intensified concern about overdiagnosis of prostate cancer, that is, detection of cancer that would have remained silent and caused the patient no illness throughout his lifetime.[2,4]

In May 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in healthy men of all ages, concluding that the harms of screening outweigh the benefits (Grade D recommendation).[6] This recommendation, however, remains controversial among health care professionals. Potential benefits of regular PSA screening include early cancer detection and reduced mortality rates. Potential harms include anxiety related to abnormal results, pain, infection, and bleeding due to diagnostic biopsies.[7-10]

Landmark trials, including the European Randomized Study of Screening for Prostate Cancer (ERSPC), the Göteborg trial (from the Swedish center in the ERSPC trial), and the U.S.-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial have published findings on the effect of PSA screening on prostate cancer mortality. Both the ERSPC and PLCO trials found little effect on mortality following PSA screening.[11] The Göteborg trial reported a 0.40 percent absolute risk reduction in prostate cancer mortality, a relative risk reduction of 44

percent, and no difference in overall mortality in men aged 50 to 64 over 14 years of screening.[12] Citing these trials, the USPSTF assessed the potential benefit of screening to be zero to one death from prostate cancer prevented for every 1,000 men aged 55 to 69 screened by PSA testing every 1 to 4 years for 10 years. They also estimated that there would be 100 to 120 men with false-positive tests and 110 men with true-positive tests; among the latter, rates of complications from treatment would range from fewer than 1 death per 1,000 men to 29 cases of erectile dysfunction per 1,000 men screened and treated.[6] For these reasons, determining which men with clinically localized prostate cancer are most likely to benefit from interventions such as surgery and radiation could potentially improve the balance of benefits and harms, especially in those identified by screening. Current practice is to use tumor grade as the primary prognostic variable in patients with clinically localized prostate cancer.[2] After biopsy confirms the presence of the cancer, pathologists report tumor grade in terms of the Gleason score, which ranges from 2 to 10.[4] Gleason 8–10 tumors are considered the most aggressive, Gleason 7 tumors are considered somewhat less aggressive, and Gleason 6 or lower tumors are considered potentially indolent.[13] Although the primary measure of tumor aggressiveness is the Gleason histologic score, efforts are under way to identify more reliable prognostic factors.

Staging is the process of assessing whether the cancer is confined within the prostate gland or has spread beyond and, if so, to what extent it has spread.[4] 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). The staging system currently used is the American Joint Committee on Cancer TNM classification.[4] The TNM classification is based on the extent of primary tumor (T stages), whether cancer has spread to the adjacent lymph nodes (N stages), and any metastasis (M stages).[4,14] These classifications are detailed in Table 1, Table 2, and Table 3.

Table 1. Tumor (T) stages

Stage	Description
T1	The tumor cannot be felt or seen using imaging techniques
	T1a. The cancer cells are incidentally found in 5% or less of resected tissue
	T1b. The cancer cells are found in more than 5% of the resected tissue
	T1c. The cancer is identified by needle biopsy, which is performed because of high prostate-specific antigen levels
T2	The cancer is confined to the prostate but can be felt as a small, well-defined nodule
	T2a. The cancer is in half of a prostate lobe
	T2b. The cancer is in more than half of a prostate lobe
	T2c. The cancer is in both prostate lobes
T3	The tumor extends through the prostate capsule
	T3a: The cancer extends outside the prostate but not to the seminal vesicles
	T3b: The cancer has spread to the seminal vesicles
T4	The tumor is fixed or invades adjacent structures

Table 2. Lymph node (N) stages

Stage	Description
NX	Nearby lymph nodes were not assessed
N0	The cancer has not spread to any nearby lymph nodes
N1	The cancer has spread to one or more nearby lymph nodes in the pelvis

Table 3. Metastasis (M) stages

Stage	Description
M0	The cancer has not spread past nearby lymph nodes
M1	The cancer has spread beyond nearby lymph nodes
	M1a: The cancer has spread to distant (outside the pelvis) lymph nodes
	M1b: The cancer has spread to bone
	M1c: The cancer has spread to other organs such as the lungs, liver, or brain (with or without spread to the bones)

Because of the limited sensitivity of pretreatment evaluations, some men who have received a diagnosis of clinically localized prostate cancer may actually have cancer that has spread outside the prostate gland. Unfortunately, additional assessments such as radiographs, bone scans, computed tomography (CT), and magnetic resonance imaging (MRI) are of limited use, particularly for detecting small foci of cancer in lymph nodes. Several methods for improving detection via imaging are under study. For detecting cancer in the lymph nodes, an innovative technique called enhanced MRI may help.[14] For identifying prostate cancer in other parts of the body, a new type of positron-emission tomography scan that uses the radioactive tracer carbon acetate as a replacement for fluorodeoxyglucose may be useful; it may also be used to define the effectiveness of the therapy.[14]

The TNM categories are combined with the Gleason histologic score and PSA results (stage grouping) to determine the overall stage, which is commonly reported in Roman figures (Stages I, IIA, IIB, III, and IV), with stage I being the least advanced and stage IV being the most advanced. In the absence of a Gleason histologic score, staging can still be based on the TNM classification. The criteria for Stages I and II are provided in Table 4 below:

Table 4. Anatomic and prognostic staging

Stage Group	T*	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA<20	Gleason 7
	T1a–c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason ≤7
IIB	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8

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*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2. X=unknown

Another categorization incorporating PSA levels, Gleason histologic score, and TNM stage stratifies tumors into low-, intermediate-, and high-risk (in terms of their likelihood of progressing with no treatment or recurring after early intervention).[4]

- Low risk (corresponding to stage I): a PSA level of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage of T1c or T2a

- Intermediate risk (roughly corresponding to stage IIA): a PSA level of 10–20 ng/mL, a Gleason score of 7, or a clinical stage of T2b but not qualifying for high risk
- High risk (roughly corresponding to stage IIB): a PSA level of more than 20 ng/mL, a Gleason score of 8–10, or a clinical stage of T2c

Clinicians make pretreatment assessment of whether prostate cancer is localized by determining tumor stage, basing their decision on a clinical examination (principally by digital rectal examination). Prostate cancer that is believed to be confined to the prostate gland (T1–T2, NX, M0; or stage I–II) is considered clinically localized[4] and is the focus of this report.

Therapies for Clinically Localized Prostate Cancer

The primary goal of treatment of clinically localized prostate cancer is to target the men most likely to need intervention to prevent disability or death while minimizing intervention-related complications. Treatment options that are frequently used include the following, which are described in Table 5:

- Radical prostatectomy, including laparoscopic or robotic-assisted prostatectomy
- External beam radiotherapy (EBRT), including conventional radiation, intensity-modulated radiation, three-dimensional (3D) conformal radiation, stereotactic body radiation therapy, and proton beam radiation
- Interstitial brachytherapy
- Cryotherapy
- Androgen deprivation therapy
- Watchful waiting
- Active surveillance
- High-intensity focused ultrasound

Table 5. Treatment options for clinically localized prostate cancer

Treatment Option	Treatment Description
Radical prostatectomy (open retropubic, open perineal, laparoscopic, robotic-assisted approaches)	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes
EBRT, including conventional radiation, intensity-modulated radiation, 3D conformal radiation, proton beam, and stereotactic body radiation therapy	Multiple doses of radiation from an external source applied over several days to weeks
Interstitial brachytherapy	Radioactive implants placed using radiologic guidance. Low-dose-rate/permanent implants and high-dose-rate brachytherapy may be used. Combination therapy comprises EBRT with a brachytherapy boost
Cryoablation	Destruction of cells through rapid freezing and thawing, using transrectal guided placement of probes and injection of freezing/thawing gases
Androgen deprivation therapy	Oral or injection medications or surgical removal of testicles to lower or block circulating androgens
Watchful waiting	Relatively passive patient followup, with symptom management if and when any symptoms occur[3]

Treatment Option	Treatment Description
Active surveillance	Usually includes hands-on followup in which prostate-specific antigen levels are checked, prostate biopsies may be repeated, and subsequent treatment is planned[3]
High-intensity focused ultrasound therapy	Tissue ablation of the prostate by intense heat, focusing on the identified cancerous area

3D = three-dimensional; EBRT = external beam radiation therapy

Choice of treatment options may be influenced by factors such as patient age and health at the time of the diagnosis, life expectancy, estimated likelihood of cancer progression without treatment, the surgeon's experience and preference, and treatment-related convenience, costs, and potential for eradication and adverse effects (e.g., incontinence, sexual dysfunction).[4] Before choosing any intervention, an assessment of the overall health status of patients is important because it may influence response to therapy, severity of complications, and life expectancy.[4]

The treatment for men with clinically localized prostate cancer has been the subject of much debate. As discussed above, identifying those men most likely to benefit from aggressive therapy is challenging. Ideally, those with slowly progressing disease who are more likely to die of other causes would be spared unnecessary treatment, while those men with aggressive localized prostate cancer would be offered curative procedures.[3,10] One option currently under study for assessing disease progression is an approach called "active surveillance," which typically includes monitoring of PSA levels and rate of increase, periodic digital rectal examination, and repeat prostate biopsies.

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health (NIH) State-of-the Science Conference in December 2011 to better understand the risks and benefits of active surveillance and other observational management strategies for PSA-screening–detected, low-grade, localized prostate cancer.[3] The panel members concluded that active surveillance should be offered to patients with low-risk prostate cancer.

The NIH panel used the term "watchful waiting" to describe a palliative observational strategy—that is, waiting for symptoms to appear and then intervening to manage the symptoms. In the 2008 comparative effectiveness review (CER) that we are updating, "Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer," these two approaches were considered together.[15] In the literature, the distinction between active surveillance (with curative intent) and other observational strategies (with palliative intent) has not always been clear; however, for this systematic review update we will attempt to separate the two using the definitions proposed at the NIH State-of-the-Science Conference in 2011.[3]

Findings from the Original Report

The 2008 CER on therapies for clinically localized prostate cancer, written by the University of Minnesota Evidence-Based Practice Center (EPC), included 18 randomized controlled trials (RCTs) and 473 observational studies.[15] None of the included studies enrolled patients with prostate cancer primarily identified by PSA testing. The main findings of the 2008 report include the following:

- No single therapy can be considered the preferred treatment for localized prostate cancer because of limitations in the body of evidence as well as the likely trade-offs a 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 across treatments.
- No RCT reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity.
- The results from the analysis of national administrative databases and surveys suggested that provider/hospital characteristics, including radical prostatectomy procedure volume, physician specialty, and geographic region, affect outcomes. Patient outcomes varied in different locations and were associated with provider and hospital case volume, independent of patient and disease characteristics. Screening practices and treatment choices varied by physician specialty and across regions of the United States. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels.
- Few data exist on the comparative effectiveness of treatments based on stratification of risk into low, intermediate, and high categories using PSA levels, histologic score, and tumor volume.

Overall, the authors concluded that "assessment of the comparative effectiveness and harms of localized prostate cancer treatments is difficult because of limitations in the evidence."[15] For example, only a few RCTs directly compared the effectiveness between (rather than within) major treatment categories. Additionally, many of these RCTs were inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the primary outcomes. Finally, some RCTs were conducted before prostate cancer detection with PSA testing was available.

Some of the remaining issues and future research needs that were outlined in the 2008 report included the following[15]:

- RCTs should evaluate relative effectiveness and adverse events and stratify their findings based on patient (e.g., age, race, comorbidity) and tumor (e.g., level of PSA, stage, histologic grade) characteristics.
- Comparative trials on technologies that were considered to be "emerging" at the time the report was written—intensity-modulated radiotherapy, proton beam radiation, cryotherapy, and robotic-assisted and laparoscopic prostatectomy—must provide long-term followup data.
- Head-to-head RCTs must be adequately powered to compare primary treatments for localized prostate cancer.
- Trials should standardize reporting of key clinically relevant outcomes and should structure the assessment of outcome measures such as quality of life and health status.

Rationale for Update

A surveillance analysis conducted by the Southern California EPC in May 2012 determined the need for this update. In the analysis, investigators evaluated the Key Questions (KQs) from the 2008 CER and conducted a restricted literature search for new evidence.[16] The key finding of the analysis was that the Prostate Cancer Intervention Versus Observation Trial (PIVOT),[16-18] published after the 2008 report, makes its conclusions out of date. Specifically, the analysis suggested that KQs 1, 2, and 4 should be reevaluated, as newly available evidence from the

PIVOT trial and other recent studies may change the conclusions from those of the previous report.[16]

II. Scope and Key Questions

This update examines the same four KQs as in the original 2008 report on the comparative effectiveness of treatments for clinically localized prostate cancer. Although these KQs were reviewed and approved by the Agency for Healthcare Research and Quality (AHRQ) and discussed with Technical Expert Panel (TEP) members for the original report, we presented them for discussion with a newly convened TEP for this update and made changes as necessary. This update will summarize the more recent evidence comparing the relative effectiveness and safety of treatment options for clinically localized prostate cancer. The KQs we will address are as follows:

Key Question 1

What are the comparative risks and benefits of the following therapies for clinically localized prostate cancer?

a. Radical prostatectomy, including open (retropubic and perineal) and laparoscopic (with or without robotic assistance) approaches
b. EBRT, including standard therapy and therapies designed to decrease exposure to normal tissues such as 3D conformal radiation therapy, intensity-modulated radiation therapy, proton beam therapy, and stereotactic body radiation therapy
c. Interstitial brachytherapy
d. Cryosurgery
e. Watchful waiting
f. Active surveillance
g. Hormonal therapy as primary therapy, adjuvant, or neoadjuvant to other therapies
h. High-intensity focused ultrasound

Key Question 2

How do specific patient characteristics (e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences such as trade-off of treatment-related adverse effects vs. potential for disease progression) affect the outcomes of these therapies overall and differentially?

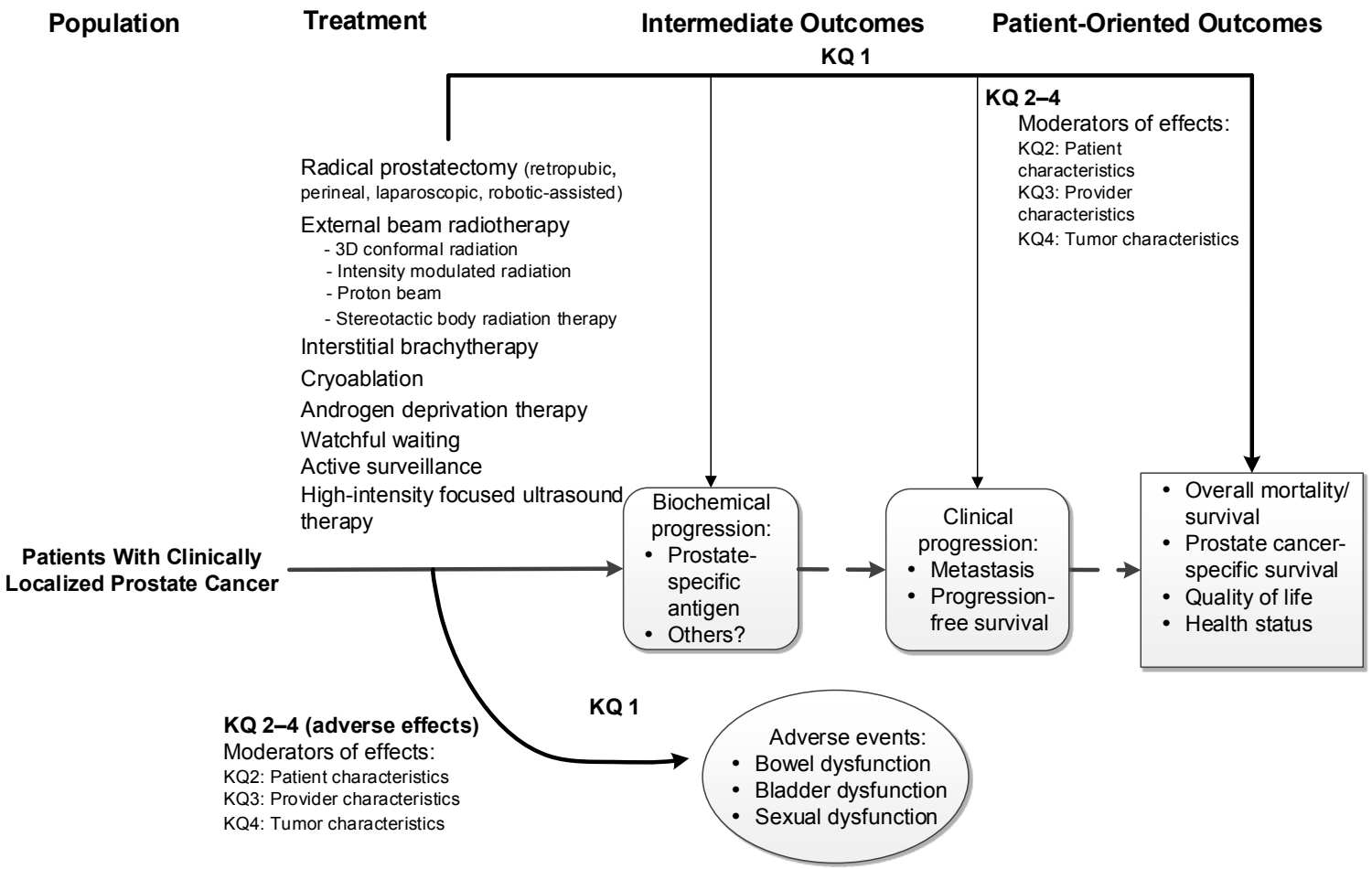
Key Question 3

How do provider/hospital characteristics affect outcomes of these therapies overall and differentially (e.g., geographic region, case volume, learning curve)?

Key Question 4

How do tumor characteristics (e.g., Gleason score, tumor volume, screen-detected vs. clinically detected tumors, and PSA levels) affect the outcomes of these therapies overall and differentially?

III. Analytic Framework



3-D, Three-dimensional; KQ: key question

IV. Methods

This section documents the methods we will use to conduct and produce this updated systematic review on therapies for clinically localized prostate cancer for AHRQ through its Effective Health Care Program (www.effectivehealthcare.ahrq.gov).

The methods used for preparing the 2008 CER report were developed through a rigorous process by the University of Minnesota EPC in consultation with AHRQ and a TEP.[15] We incorporated the methods from the original report where possible. However, for this update, our methods were informed by a more recent version of the guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[19] hereafter referred to as the *Methods Guide*. The search strategy will be based on that composed for the 2008 report but will incorporate newer search methods and will reflect changes in the relevant nomenclature, such as differentiating active surveillance from watchful waiting. We will use similar criteria and methods as in the 2008 report for study selection, data extraction, and risk-of-bias assessment for studies published since January 2007. The strength of evidence for each outcome will be assessed according to more recent guidance from the *Methods Guide*.[19]

A. Criteria for Inclusion/Exclusion of Studies for This Review Update

Study Design and Reporting Criteria

We plan to use the same study selection criteria as in the 2008 report (see Table 6, 7, 8 and Table 9). For KQs 1, 2, and 4, we will include randomized trials only if the randomized treatment allocation was based on men with clinically localized disease and if clinical outcomes are reported for T1 and T2 disease separately from T3 and T4 disease. In the absence of any randomized trials, large nonrandomized comparative studies will be considered for inclusion.

For KQ 3, we will include multicenter or comparative observational studies that examined the effect of provider characteristics on the diagnosis and treatment of localized prostate cancer.

Non-English-language studies will be excluded. Moher et al.[20] have demonstrated that exclusion of non–English-language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.[21] found that non-English-language studies typically were of lower methodological quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non–English-language studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary to translate studies to identify those of acceptable quality for inclusion in our review.[20,21]

Table 6. Inclusion criteria: Key Question 1

Question Components	Inclusion Criteria
Major treatment options of interest: • Radical prostatectomy (retropubic, perineal, laparoscopic, robotic-assisted) • External beam radiotherapy • Interstitial brachytherapy • Primary androgen deprivation • Watchful waiting and active surveillance **Emerging treatment options of interest:** • Cryotherapy • High-intensity focused ultrasound therapy (Pre-marketing Approval Application for one device currently under consideration by the U.S. Food and Drug Administration) • Proton beam therapy • Stereotactic body radiation therapy **Outcomes of interest:** • Overall mortality and morbidity • Prostate-related mortality and morbidity • Quality of life • Adverse effects such as urinary incontinence and sexual dysfunction	Randomized controlled trials (RCTs) comparing different treatment options that enrolled patients with clinically localized disease and reported outcomes of interest with duration of followup ≥ 1 yr. Trials must focus on, or provide separate analyses for, subjects with localized disease (T1/T2). RCTs that assigned treatments based on pathological staging (i.e., based on intraoperative findings) rather than clinical staging will be excluded. If no RCTs are available, we will consider large nonrandomized comparative studies that enrolled consecutive patients. For any nonrandomized comparative studies, we will include 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. For adverse events, we will also include large nonrandomized comparative studies that reported relevant data. Studies could be prospective or retrospective; however, to reduce the risk of bias, retrospective studies must have used consecutive enrollment or enrollment of a random sample of eligible participants. Studies must have been published in English.

Table 7. Inclusion criteria: Key Question 2

Question Components	Inclusion Criteria
Effectiveness outcomes according to patient age, race/ethnicity, comorbid conditions, and preferences	Studies that meet the inclusion criteria for Key Question 1 and report outcomes stratified according to patient characteristics

Table 8. Inclusion criteria: Key Question 3

Question Components	Inclusion Criteria
• Association between provider specialty and prostate cancer management • Association between physician characteristics and patient outcomes • Association between geographic region and outcomes • Association between hospital and provider case volume and outcomes	Studies using administrative data that measured outcomes in different locations, administrative surveys that measured physician distribution in U.S. regions, and epidemiologic studies that evaluated the association between provider characteristics and patient outcomes with a control group. Studies will be excluded if there was no information regarding provider characteristics or if they were single-hospital studies with no control comparisons that did not test an associative hypothesis.

Table 9. Inclusion criteria: Key Question 4

Question Components	Inclusion Criteria
Effectiveness outcomes according to tumor characteristics (prostate-specific antigen, tumor stage, histologic grade, tumor risk strata)	Studies that meet the inclusion criteria for Key Question 1 and report outcomes stratified according to tumor characteristics

PICOTS Criteria

Population

- KQs 1, 2, 3, and 4: Men considered to have clinically localized prostate cancer (T1 to T2, N0 to X, M0 to X) regardless of age, histologic grade, or PSA level. Articles will be excluded if men with disease stage higher than T2 were enrolled, and outcomes were not stratified by stage.

Interventions

- For KQs 1, 2, 3, and 4, we will include treatment options for men with clinically localized prostate cancer: radical prostatectomy (including retropubic, perineal, laparoscopic, robotic-assisted), watchful waiting, active surveillance, EBRT (including conventional radiation, IMRT, 3D conformal radiation, proton beam, and stereotactic body radiation therapy), brachytherapy, androgen deprivation therapy, high-intensity focused ultrasound, and cryotherapy.

Comparators

- Any of the interventions of interest above or watchful waiting.

Outcomes

- The primary outcome is overall mortality or survival. Additional outcomes include prostate-cancer–specific mortality or survival, biochemical (PSA) progression, metastatic and/or clinical progression-free survival, health status, and quality of life. We will focus primarily on common and severe adverse events of treatment including bowel, bladder, and sexual dysfunction, as well as harms from biopsy such as bleeding and nosocomial infections.
- For KQ 3, we plan to examine outcomes after radical prostatectomy, the most common treatment for localized prostate cancer, in association with provider location, case volume, and affiliation with academic centers.

Timing

- Duration of followup will be appropriate for the outcome under consideration.

Settings

- No restrictions by setting.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Literature searches (see Table 10) will be performed by medical librarians and will follow established systematic search protocols. For all KQs, we will search the following databases on the OVID SP platform using the one-search and deduplication features: MEDLINE®, PreMEDLINE, and EMBASE®. We will also search The Cochrane Library (including the Central Register of Controlled Trials, the Cochrane Database of Methodology Reviews, and the Cochrane Database of Systematic Reviews), the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, gray literature, and the U.K. National Health Service Economic Evaluation Database for unique reviews, trials, economic analyses, and technology assessments. We will use resources available through the EPC Scientific Resource Center (SRC) to access Scientific Information Packets.

Search terms will be identified by the following: (1) reviewing relevant systematic reviews on similar topics that are identified by the research staff; (2) reviewing how other relevant studies are indexed, their subject heading terms, and their keywords; and (3) reviewing MeSH® and EMTREE indexes for relevant and appropriate terms. We will then identify a combination of subject headings and keywords and develop search strategies using these terms. Once developed, search strategies will be reviewed by senior research analyst(s) and senior medical librarians. A study-design filter will be applied to retrieve systematic reviews and ongoing clinical trials. Details (specific search terms and search strategies) are provided in Appendix A of this protocol.

Table 10. Electronic database searches

Name	Date Limits	Platform/Provider	Strategy
The Cochrane Central Register of Controlled Trials (CENTRAL)	2007 - current	Wiley	See below
The Cochrane Database of Methodology Reviews (Methodology Reviews)	2007 - current	Wiley	
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	2007 - current	Wiley	
Cumulative Index of Nursing and Allied Health Literature (CINAHL®)	2007 - current	EBSCOhost	
Database of Abstracts of Reviews of Effects (DARE)	2007 - current	Wiley	
EMBASE® (Excerpta Medica)	2007 - current	OvidSP	
Health Technology Assessment Database (HTA)	2007 - current	Wiley	
MEDLINE®	2007 - current	OvidSP	
PubMed® (In-process and publisher records)	2007 - current	National Library of Medicine	
U.K. National Health Service Economic Evaluation Database (NHS EED)	2007 - current	Wiley	
Gray Literature Resources			
ClinicalTrials.gov	2007 - current	National Institutes of Health	
Centers for Disease Control and Prevention (CDC)	2007 - current	CDC	
Centers for Medicare and Medicaid (CMS) - Medicare Coverage Database	2007 - current	CMS	
Internet	2007 - current	Google	
Manufacturers	2007 - current	Company name	
Medscape	2007 - current	WebMD®	
National Guideline Clearinghouse™ (NGC)	2007 - current	Agency for Healthcare Research and Quality	
U.S. Food and Drug Administration (FDA), including Medical Device databases/Drugs@FDA	2007 - current	FDA	

Note. The search period will be 2007 to the present in all databases.

The medical librarian will initially review the literature search results. Using the KQs and inclusion/exclusion criteria identified by senior research analysts, the medical librarian will assess relevancy and retrieve results. Feedback from the senior research analysts and the senior medical librarian—including details regarding gaps in the search strategy and articles identified by the senior research analysts but not retrieved by the searches—will be integrated into the search strategy using key terms and subject headings. The updated strategy will be rerun in all identified databases. Additional results will be scanned, and medical librarians will assess their relevancy. New results will be downloaded and forwarded to senior research analysts for review. Hand searches of reference lists in identified articles will also be reviewed for possible inclusion. The search will be updated during peer review of the draft report.

Articles will be reviewed at the abstract level in duplicate, and any articles possibly meeting the inclusion criteria for at least one KQ will be obtained for full review. If there are disagreements between both reviewers, a third reviewer will resolve the issue.

Full articles will be screened in duplicate, and any meeting the inclusion criteria will be retained for abstraction of information on general study characteristics, patient characteristics, treatment characteristics, risk-of-bias items, and outcome data (see the next section).

A. Data Abstraction and Data Management

We plan to use the DistillerSR® (Evidence Partners Inc., Ottawa, Ontario, Canada) Web-based systematic review software for abstract screening and data extraction. Each team member's data extraction will be reviewed by one other team member. Also, because of the possibility of subjective interpretation, the risk-of-bias items will be judged in duplicate. We will resolve all discrepancies through discussion. Two researchers will extract study, patient, tumor, and intervention characteristics and predefined outcomes onto standardized forms. Standard errors, regression coefficients, and 95-percent confidence interval (95% CI) will be calculated from reported means, standard deviations, and sample size when provided/appropriate.[22] Multiple publications of the same study (e.g., publications reporting subgroups, other outcomes, longer followup) will be identified by examining author affiliations, study designs, enrollment criteria, and enrollment dates. We will contact study authors as necessary to clarify any uncertainty about the independence of two or more articles. If we determine that important information seems to be missing from the available results of a study, or if we are aware of unpublished or significant in-press data, we will request additional information from the authors.

B. Assessment of Methodological Risk of Bias of Individual Studies

As stated above, because of the possibility of subjective interpretation, assessment of methodological risk of bias of individual studies will be performed by two researchers for each study, and discrepancies will be resolved by consensus. If consensus cannot be reached, a third researcher will adjudicate. We will assess the risk of bias by following the guidelines in the chapter, "Assessing the Risk of *Bias of Individual Studies When Comparing Medical Interventions" in the Methods* Guide.[23]

For KQs 1, 2, and 4, we will assess the risk of bias for the RCTs by evaluating several variables revised from the 2008 report. In addition, we will assess fidelity to the protocol to address performance bias and blinding of outcome assessors to address detection bias when outcomes are subjective (as defined in Table 11). Each of these items will be answered "Yes," "No," or "Not reported."

Table 11. Risk of bias of randomized controlled studies

Item	Comment
1. Was there concealment of group allocation?	—
2. Were data analyzed based on the intention-to-treat-principle?	—
3. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	—

Item	Comment
4. Was the outcome measure of interest objective and was it objectively measured?	The following will always be considered objective outcomes: overall mortality or survival, prostate cancer-specific survival, adverse events, biochemical free progression survival, hospital stay, and office visits. The following will always be considered subjective outcomes: quality of life and health status.
5. Was there a 15 percent or less difference in the length of followup for the two groups?	—
6. Did 85 percent or more of enrolled patients provide data at the time point of interest?	—
7. Was there fidelity to the protocol?	—

We will categorize each study as having low, medium, or high risk of bias using the following method:

- To be considered as having low risk of bias, the study must meet all the following conditions:
  - There was concealment of allocation.
  - Data analysis was based on the intention-to-treat-principle.
  - If outcome assessors were not blinded (item 3) or blinding of outcome assessors was not reported, then the outcome must have been objective (item 4).
  - There was a difference of 15 percent or less in the length of followup for the two groups.
  - Eighty-five percent or more of enrolled patients provided data at the time point of interest.
  - There was good fidelity to the protocol
- To be considered as having high risk of bias, the study must meet at least one of the following criteria:
  - The trial did not have a difference of 15 percent or less in the length of followup for the two groups.
  - The trial did not have good fidelity to the protocol.
  - Not a blinded outcome assessor (item 3) and a subjective outcome (item 4)
- To be considered as having medium risk of bias, the study neither meets the criteria for low risk of bias nor the criteria for high risk of bias.

For nonrandomized studies, risk of bias will be assessed by evaluating the variables listed in Table 12. Given the intrinsic selection bias in nonrandomized studies, we will not categorize any study as low risk of bias. Instead, we will categorize each study as having either medium or high risk of bias. To be considered as having medium risk of bias, the study must have a "yes" answer for at least three items in Table 12. Otherwise, the study will be considered to have high risk of bias.

Table 12. Risk of bias for nonrandomized studies*

Item	Comment
1. In prospective studies, was the difference in the length of followup between the groups 15 percent or less, or in case-control studies, was the time period between the treatment and outcome the same for cases and controls?	—

Item	Comment
2. In nonrandomized trials, were the outcome assessors blinded to the treatment status of participants?	By default, we will give a "no" answer to each observational study.
3. Was the outcome measure of interest objective and was it objectively measured?	The following will always be considered objective outcomes: overall mortality or survival, prostate cancer-specific survival, adverse events, biochemical free progression survival, hospital stay, and office visits. The following will always be considered subjective outcomes: quality of life and health status.
4. In nonrandomized trials, did the study maintain fidelity to the intervention protocol?	By default, we will give a "no" answer to each observational study.

*We will include only nonrandomized studies that use consecutive enrollment and a design or analysis control accounting for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches.

For KQ 3, we plan to use the same rating system as described in the 2008 report to assess risk of bias. Risk-of-bias assessment will be scored from 0 (poorest) to 5 (highest).[24] Summated scores will be used to establish study risk of bias.

C. Data Synthesis

Because of differences in study designs, treatments, patient and tumor characteristics, and reporting of outcomes, the 2008 report did not pool studies for KQs 1, 2, and 4. In this update, we plan to perform meta-analysis wherever possible and appropriate, basing our decision on the data in our included studies. This decision, however, will depend on the judged homogeneity of the different study populations, cointerventions, and outcomes. Summaries of effectiveness and adverse-event outcomes with ranges according to treatment option, tumor characteristics, and group sample size will be provided. Results will be provided separately for randomized trials and nonrandomized studies.

For KQ 3, the impact of the provider or hospital characteristics on clinical outcomes will be estimated by analyzing published evidence. We will describe studies of the associations between outcomes and provider and hospital characteristics and provide a qualitative synthesis of the data.

We will summarize the results of individual studies with relation to sample size and the 95% CI. Odds ratios and the 95% CIs will be calculated with random effects models.[25] If meta-analyses are possible, meta-regression models will be used to analyze possible interactions with the year of data collection, data source to measure outcomes, and adjustment for confounding factors.[26,27] The calculations will be performed using STATA®[28] (StataCorp LP, College Station, TX) and Comprehensive Meta-Analysis[25] (Biostat, Inc., Englewood, NJ) software. Consistency in the results will be tested by comparing the direction of effects. We will use I-squared[29] and tau[30] tests to assess heterogeneity in study results.

Rating the Strength of the Body of Evidence

We plan to provide evidence ratings (see Table 13) for the following outcomes: overall mortality or survival, prostate cancer-specific survival, quality of life, health status, and harms (bowel, bladder, and sexual dysfunction). We will assess strength of evidence by following the guidelines from the chapter, "Grading the Strength of a Body of Evidence When Comparing Medical Interventions," in the *Methods Guide*.[19] We will grade the strength of evidence for each major health outcome according to the following:

- Risk of bias (low, medium, or high)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)

We will assess reporting bias by examining the following:

- Whether any trials registered at the ClinicalTrials.gov database have passed the completion dates but have not been published within 2 years of completion
- Whether studies with smaller sample sizes tend toward positive or negative assessments of treatment for localized prostate cancer
- Whether studies funded by different sources report treatment effects in different directions or sizes
- Whether several trials do not report a particular outcome that is considered important

The strength of evidence will be allotted an overall grade of high, moderate, low, or insufficient (see Table 13).

Table 13. Strength-of-evidence grade for the body of evidence

Grade	Evidence-based Practice Center Program Definition
High	High confidence that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect.
Insufficient	Evidence is either unavailable or does not permit a conclusion.

D. Assessing the Applicability of the Evidence for Each Key Question

Applicability will be assessed by following the guidelines in the chapter, "Assessing the Applicability of Studies When Comparing Medical Interventions," in the *Methods Guide*.[31] The applicability of the evidence involves the following of five aspects: patients, interventions, comparisons, outcomes, and settings. We will address factors relevant to the applicability of the evidence by evaluating patient selection in both observational studies and clinical trials. We will consider the primary biology and epidemiology (grade and stage of the prostate cancer) and the present-day clinical practice setting. The typical interventions, comparisons, outcomes (e.g., overall mortality, prostate cancer-specific survival), and settings of care will also be used to more clearly specify the most applicable study characteristics (i.e., most typical of localized prostate cancer care in the United States).

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VI. Definition of Terms

I^2: This is a measure of heterogeneity, ranging from 0 to 100 percent, in which higher values suggest greater heterogeneity. See Higgins and Thompson[29] for more details.

Tau: This is a measure of heterogeneity indicating the standard deviation of the effect sizes; it is on the scale of the effect size. For example, in a meta-analysis of log odds ratio, tau is on the scale of the log odds ratio. See Rucker et al.[30] for more details.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, and outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and will not review the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest of more than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer-review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer-review comments are documented and will, for CERs and Technical Briefs, be published 3 months after publication of the Evidence Report.

Potential Reviewers must disclose any financial conflicts of interest of more than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

X. EPC Team Disclosures

There are no conflicts of interest among the EPC team. One team member is a genitourinary radiation oncologist who treats patients with prostate cancer, and another is a urologic oncologist.

XI. Role of the Funder

This project is funded under Contract No. HHSA 290-2012-00011i from AHRQ, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by AHRQ or the U.S. Department of Health and Human Services.

XII. Appendix A. Literature Search Methods

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider	Strategy
Bibliographic Databases			
The Cochrane Central Register of Controlled Trials (CENTRAL)	2007–current	Wiley	See below
The Cochrane Database of Methodology Reviews (Methodology Reviews)	2007–current	Wiley	
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	2007–current	Wiley	
Cumulative Index of Nursing and Allied Health Literature (CINAHL®)	2007–current	EBSCOhost	
Database of Abstracts of Reviews of Effects (DARE)	2007–current	Wiley	
EMBASE® (Excerpta Medica)	2007–current	OvidSP	
Health Technology Assessment Database (HTA)	2007–current	Wiley	
MEDLINE®	2007–current	OvidSP	
PubMed® (In-process and Publisher records)	2007–current	NLM	
U.K. National Health Service Economic Evaluation Database (NHS EED)	2007–current	Wiley	
Gray Literature Resources			
ClinicalTrials.gov	2007–current	NIH	
Centers for Disease Control and Prevention (CDC)	2007–current	CDC	
Centers for Medicare and Medicaid (CMS) - Medicare Coverage Database	2007–current	CMS	
Internet	2007–current	Google	
Manufacturers:	2007–current	Company name	
Medscape	2007–current	WebMD®	
National Guideline Clearinghouse™ (NGC)	2007–current	AHRQ	
U.S. Food and Drug Administration (FDA), including Medical Device databases/Drugs@FDA	2007–current	FDA	

Detailed search strategies are presented below.

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in the ECRI Institute's collections will be routinely reviewed. Relevant gray literature, including nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies, will be screened in addition to available documents from educational facilities, consulting firms, and corporations. Other mechanisms to retrieve additional relevant information will include review of bibliographies/reference lists from peer-reviewed and gray literature.

Medical Subject Headings (MeSH®), EMTREE, and Keywords

The search strategies employed combinations of free-text keywords and controlled vocabulary terms including (but not limited to) the concepts shown in the Topic-specific Search Terms table below.

Topic-specific search terms

Concept	Controlled Vocabulary	Keywords
Prostate cancer	EMBASE (EMTREE) Neoplasms/ Prostate/ Prostatic Neoplasms/	Cancer* Carcinoma* Neoplasm* Prostat*
Treatment options	EMBASE (EMTREE) Brachytherapy/ Cryosurgery/ Cryotherapy/ Freezing/ High-Intensity Focused Ultrasound Ablation/ Prostatectomy/ exp Radiotherapy/ Watchful Waiting/	Active surveillance Androgen deprivation Brachytherap* Cryoablat* Cryosurger* Cryotherap* Curietherap* EBRT Freez* HIFU High intensity focused ultrasound IMRT LRP Prostatectom* Proton Radiotherap* Radiation RLRP Watchful waiting

Search Strategies

The strategy below is presented in Ovid syntax; the search will be simultaneously conducted across EMBASE and MEDLINE. A similar strategy will be used to search the databases composing the Cochrane Library.

Ovid Conventions

$ or * = truncation character (wildcard)
ADJ*n* = search terms within a specified number (*n*) of words from each other in any order
exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de. = limit controlled vocabulary heading
.fs. = floating subheading
.hw. = limit to heading word
.mp. = combined search fields (default if no fields are specified)
.pt. = publication type
.ti. = limit to title
.tw. = limit to title and abstract fields

EMBASE/MEDLINE
Ovid Syntax

Set #	Concept	Search Statement
1	Prostate cancer	Prostatic Neoplasms/
2	Prostate cancer	(prostat$.ti,ab. or Prostate/) AND (cancer.ti,ab. or Neoplasms/ or neoplasm$ or carcinoma$)
3	Combine sets	S1 OR S2
4	Treatment options	watchful waiting.ti,ab. or Watchful Waiting/ or active surveillance.ti,ab. or prostatectom$.ti,ab. or Prostatectomy/ or LRP.ti,ab. or RLRP.ti,ab. or exp Radiotherapy/ or radiotherap$.ti,ab. or EBRT.ti,ab. or IMRT.ti,ab. or brachytherap$.ti,ab. or Brachytherapy/ or curietherap$.ti,ab. or cryosurger$.ti,ab. or Cryosurgery/ or cryotherap$.ti,ab. or Cryotherapy/ or cryoablat$.ti,ab. or Freezing/ or freez$.ti,ab. or androgen deprivation.ti,ab. or High-Intensity Focused Ultrasound Ablation/ or high intensity focused ultrasound.ti,ab. or HIFU.ti,ab. or (high and intensity and focused and ultrasound).ti,ab.
5	Publication types	(Randomized controlled trial/ or random allocation/ or double-blind method/ or single-blind method/ or placebos/ or cross-over studies/ or crossover procedure/ or cross over studies/ or double blind procedure/ or single blind procedure/ or placebo/ or latin square design/ or crossover design/ or double-blind studies/ or single-blind studies/ or triple-blind studies/ or random assignment/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies/ or intermethod comparison/ or parallel design/ or control group/ or prospective study/ or retrospective study/ or case control study/ or major clinical study/ or evaluation studies/ or follow-up studies/ or case series.ti.ab. or random$.hw. or random$.ti. or placebo$.ti,ab. or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)).ti,ab. or latin square.ti,ab. or ISRCTN$.ti,ab. or ACTRN$.ti,ab. or (NCT$ not NCT).ti,ab.)
6	Combine sets	S3 AND S4 AND S5
7	Limit	6 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
8	Limit	7 not (book/ or edited book/ or case report/ or case reports/ or comment/ or conference abstract/ or conference paper/ or conference review/ or editorial/ or letter/ or news/ or note/ or proceeding/ or (book or edited book or case report or case reports or comment or conference or editorial or letter or news or note or proceeding).pt. or ("comment/reply" or editorial or letter or review-book).pt.)
9	Limit	8 not (case report.de. OR case reports.pt. OR case report.ti. OR patient.ti. OR (year ADJ old).ti,ab.)
10	Limit	Limit 9 to English and humans and yr="2007-Current"
11	Remove duplicates	Remove duplicates from 10

Additional Conventions:

PubMed

* = truncation character (wildcard)

[tiab] = limit to title or abstract

Cochrane Library

* = truncation character (wildcard)

PubMed

Set #	Concept	Search Statement
1	Prostate cancer	"prostatic neoplasms/surgery"[mesh] or "prostatic neoplasms/therapy"[mesh] OR "prostatic neoplasms/radiotherapy"[mesh]
2	Prostate cancer	"prostatic neoplasms"[mesh] OR (prostat*[tiab] AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab]))
3	Combine sets	S1 OR S2

Set #	Concept	Search Statement
4	Treatment options	"watchful waiting"[mesh] OR "watchful waiting"[tiab] OR "active surveillance"[tiab] OR prostatectomy[mesh] OR LRP[tiab] OR RLRP[tiab] OR prostatectom*[tiab] OR "radiotherapy"[mesh] OR radiotherap*[tiab] OR EBRT[tiab] OR IMRT[tiab] OR (proton[tiab] AND radiation[tiab] AND therap*[tiab]) OR (intensity[tiab] AND modulated[tiab] AND therap*[tiab]) OR brachytherapy[mesh] OR brachytherap*[tiab] OR curietherap*[tiab] OR cryosurgery[mesh] OR cryosurger*[tiab] OR OR cryotherapy[mesh] OR cryotherap*[tiab] OR cryoablat*[tiab] OR freezing[tiab] OR "androgen deprivation"[tiab] OR "ultrasound, high-intensity focused, transrectal"[mesh] OR HIFU[tiab] OR (high[tiab] AND intensity[tiab] AND focused[tiab] AND ultrasound*[tiab])
5	Publication types	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies [pt] OR evaluation studies as topic [MH] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR meta-analysis[mh] OR meta-analysis[pt] OR outcomes research[mh] OR multicenter study[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR comparative study [tw] OR comparative studies [tw] OR evaluation study[tw] OR evaluation studies [tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebos[mh] OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
6	Combine sets	3 AND 4 AND 5
7	Limit	6 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
8	Limit	Limit 7 to: Publication date from 2007/01/01 to 2012/12/31, Humans, English

Cochrane Library

Set #	Concept	Search Statement
1	Prostate cancer	"prostate cancer" OR (prostat* AND (neoplasm* OR cancer* OR carcinoma*))
2	Treatment options	"watchful waiting" OR "active surveillance" OR LRP OR RLRP OR prostatectom* OR radiotherap* OR EBRT OR IMRT OR (proton AND radiation AND therap*) OR (intensity AND modulated AND therap*) OR brachytherap* OR curietherap* OR cryosurger* OR cryotherap* OR cryoablat* OR freezing OR "androgen deprivation" OR HIFU OR (high AND intensity AND focused AND ultrasound*)
3	Combine sets	1 AND 2
4	Limit	Limit 7 to: Publication date from 2007 to 2013