Screening for prostate cancer: research plan for systematic reviews on the benefits and harms of screening to inform an update of the 2014 Canadian Task Force on Preventive Health Care guideline

January 28, 2025

Recommendations made by the Canadian Task Force on Preventive Health Care (task force) are independent of the Canadian government. The views expressed herein do not necessarily represent the views of the Government of Canada.

Contributors:

Task Force Prostate Cancer Screening Working Group

Roland Grad (Chair), Guylène Thériault (Vice-Chair), Gail Macartney, Keith Todd, Brett Thombs and (as advisors) Philipp Dahm and Neil Bell (clinical experts).

University of Alberta ERSC (Review team)

Jennifer Pillay, Sabrina Saba, Sholeh Rahman, Nicole Gehring, Ben Vandermeer, Maria Tan, Lisa Hartling

PHAC Science Team

Casey Gray, Heather Limburg, Greg Traversy, Julie Wu

Purpose

This research plans outlines the scope and key review methods for two systematic reviews on the benefits and harms of prostate cancer screening to inform updated recommendations by the Canadian Task Force on Preventive Health Care (task force). The first review focuses on screening people not known to be at high risk with prostate-specific antigen (PSA) testing (with or without digital rectal exam (DRE)) compared with no screening or DRE alone. Studies of other interventions (e.g., DRE alone, PSA plus magnetic resonance imaging [MRI], MRI alone) compared with no screening will be considered. Comparisons with opportunistic screening (e.g., offered non-systematically during routine healthcare visits) will also be eligible but considered indirect for a no screening comparison. The second review focuses on comparisons between PSA (with or without DRE) screening and sequential screening where MRI is used to triage those with positive PSA tests to determine who receives a biopsy; studies for this review may include populations being screened or attending biopsy after screening positive with PSA.

This plan replaces the published protocol (PROSPERO CRD42022314407) for guiding the reviews commissioned by the task force to inform their guideline. The task force acknowledges the contributions made by those authors in planning the scope of the reviews. For this research plan, the key questions and eligibility criteria (Tables 1 and 2) have been adapted from the original protocol to fit the revised scope; the text describing the methods was developed anew. The revisions to the previous scope are outlined in the table footnotes. For the main question on screening versus no screening, possible outcomes were rated by the task force working group, and those rated critical (7-9 out of 9) and important (4-6 out of 9) were included. The eligible outcomes and their importance ratings have not changed for this research plan (see Table 1) with the exception of adding detection of cancer (clinically significant and nonsignificant) and biopsy referrals as important outcomes for key question (KQ) 2 (see Table 2).

Apart from these reviews on benefits and harms, the task force will commission a review on patient preferences, and treatment, for which another research plan will be created with this research plan amended. As per the GRADE Evidence-to-Decision Framework, information on resources required, equity, feasibility, and acceptability will also be considered by the task force when deciding on the strength of their recommendations and any implementation considerations.

Key Questions

The following key questions (KQs) will be answered:

KQ1: What are the benefits and harms of prostate cancer screening among people not known to be at high risk?

a) Do the benefits and harms differ by screening modality (i.e., PSA alone vs. PSA + DRE vs. DRE alone) or intensity (i.e., intervals and/or number of rounds)?

b) In screening with PSA-based strategies, do benefits and harms differ by PSA threshold value?

c) Do the benefits and harms differ by age group?

d) Do the benefits and harms differ by race, ethnicity or family history?

KQ2: What are the benefits and harms of sequential screening using MRI to target biopsies after PSA-based screening versus PSA-based screening alone?

a) Do the benefits and harms differ by age group?

b) Do the benefits and harms differ by race, ethnicity or family history?

Methods

The methods for these reviews will follow those outlined in Chapter 4 of the task force's methods guide, with a few modifications as outlined below. Reporting of the reviews will follow current reporting guidelines (PRISMA 2020) and any deviations from this plan will be described.

Eligibility criteria and subgroups of interest

Table 1. Eligibility and subgroups for KQ1 on benefits and harms of screening versus no screening

	Inclusion criteria	Exclusion criteria
Population	Individuals from the general population not selected for being at increased risk* Specific populations of interest for subgroup analyses: • Age: <55 vs. 55 to <70 vs. ≥70 years (KQ1c) • Race or ethnicity (KQ1d) • Family history: none/some (e.g., one second or higher degree relative, unspecified) vs. first-degree/strong history** (KQ1d) * For outcomes of complications from biopsy, if feasible and very low/low certainty from screening studies, we will include studies (>100 participants) limited to those getting biopsy after a positive PSA screening result **Strong history, such as (as defined by authors but more than one first degree of any age): 1) people with one brother or father or two or more male relatives with one of the following: a) diagnosed with prostate cancer at age < 60 years; b) any of whom died of prostate cancer; c) any of whom had metastatic prostate cancer. 2) family history of other cancers with two or more cancers in hereditary breast and ovarian cancer syndrome or Lynch syndrome spectrum.(Wie et al. 2023, Giri et al. 2017)	>20% <18 years. >20% high-risk for prostate cancer (i.e., working with chemicals known to be carcinogenic, known germline mutations, or strong family history**). Studies may include populations who have had a previous PSA screen (including a negative biopsy), and/ or individuals with a "normal" age-related change in urine function. Normal will be defined by clinician judgment.
Interventions	PSA +/- DRE We will also include interventions using multi-step/sequential screening strategies including PSA (e.g., risk calculation/stratification before PSA, MRI after PSA) as long as there is a comparison of no screening. DRE-alone screening Other modality used as the primary screening method (e.g., MRI only, MRI + other tests) Subgroups: • Screening strategy: PSA with vs. without DRE; PSA with vs. without additional testing apart from DRE; PSA with vs. without additional testing apart from DRE, MRI with vs. without other tests • Screening interval (KQ1a) • Number of screening rounds (KQ1a) • PSA threshold for diagnostic assessment: <4 vs. 4 ng/mL vs. >4 ng/mL vs. age-specific (KQ1b) • Type of biopsy: 6 core/sextant TRUS vs. 10-12 core TRUS vs. others (e.g., transperineal)	
Comparators	No screening (may include some opportunistic screening, i.e., initiated during a routine healthcare visit) For PSA-alone: PSA with DRE; DRE-alone (KQ1a)	
Outcomes	Potential benefits 1. Reduced prostate cancer mortality 2. Reduced all-cause mortality 3. Reduced incidence of metastatic cancer* Potential harms 4. Positive screen benign for cancer (i.e., false positive); cumulative risk (i.e., number of people with ≥1 event over 2+ rounds]) 5. Complications due to biopsy: a. mortality (shortly e.g. 30-day after biopsy and before treatment), b. severe AEs (e.g., hematuria, infections), c. serious AEs/hospitalizations (assuming one event per person if applicable), d. all complications (among all biopsies and among those benign for cancer) 6. Incontinence: a. urinary, b. bowel (risks/binary effects from patient-report ascertained actively) 7. Erectile dysfunction (risks/binary effects from patient-report ascertained actively)	

	Inclusion criteria	Exclusion criteria
	8. Overdiagnosis (all cancers and those deemed clinically important (e.g. Gleason <7 vs. ≥ 7 or International Society of Urological Pathology (ISUP) grade of 2 or higher, as defined by authors); excess number of cancers among those screened vs. not screened (will calculate if not reported but data on incidence/cumulative detection is reported) Either benefit or harm 9. Quality of life/functioning: a. generic, b. specific to cancer/prostate cancer; composite scores from scales with acceptable measurement properties (e.g., validity, reliability) 10. Psychological effects* *Reduced incidence of metastatic cancer and psychological effects were considered important, while all others were rated as critical for decision making by the task force working group	
Timing of outcome assessment	For benefits & outcome 8: minimum of 5 years after enrollment; subgroups/synthesis for short-term (e.g., 5 - <11) vs. medium-term (e.g., ≥11-<20) vs. long-term ≥20) years For outcomes: 4: after a minimum of 2 rounds of screening 5b-d: any timing; subgroups ≤30 days post-biopsy vs. longer 6, 7, 9: any timing; subgroups for short-term (e.g., ≤6 months) vs. longer-term 10: after screening, after positive screening result, after knowledge of benign results, longer term (e.g. ≥6 months) (with similar timepoints in controls)	
Setting	Settings generalizable to primary care, including organized screening programs Any country	
Study design	All outcomes: RCTs/quasi-randomized trials; nonrandomized trials (nonRCTs; exposure allocation by researchers/policy) and controlled prospective cohort studies (study designed and participant enrollment before data collection), both with concurrent controls For nonRCTs/cohorts, studies must use design or analysis methods to account for multiple confounders (e.g., age, family history) Outcomes 4 and 5: uncontrolled prospective cohorts (>100 participants) will be included for PSA screening and (if studies are located that report on 1+ benefit outcome) for other screening interventions. Subgroup analyses: i) contamination/lack of adherence (<25 vs. ≥25% in either arm e.g., < vs. ≥50% net screening in intervention arm), ii) high ROB vs. not, and iii) for outcomes 4 and 5: RCTs vs. other designs	
Publication date, type and language	No date limitations for RCTs/quasi-RCTs of PSA or DRE screening or studies on harms 2014-onwards for other study designs for benefits of PSA or DRE screening (to limit to studies most relevant to contemporary diagnostic procedures e.g. 10-12 vs. 6 core biopsies, 2014 Grading criteria, and higher use of active surveillance of low-risk cancers), and for any study design on other comparisons e.g. MRI vs. no screening Reports of final study results will be included if not peer reviewed (e.g., clinical trial registry data) Studies with full texts in English or French	Editorials, commentaries, letters, conference proceedings, government reports, narrative reviews, systematic reviews

Note: The scope of this review will differ from that described in the previously published protocol in several ways: i) added inclusion of prospective controlled studies (2014 onwards) for benefits outcomes and controlled or (in some cases) uncontrolled prospective cohorts (any dates) for harms, ii) limited specific populations for subgroup analysis to age, race, ethnicity or family history, iii) added clearly defined outcome definitions (e.g. 4 categories for complications, binary data for incontinence) and timing (e.g. minimum 2 rounds of screening offered for Positive screen benign for cancer [formerly called false positives], a minimum follow-up duration for benefits), and iv) added some pre-specified subgroup variables for interventions (e.g. number of rounds) and timing of outcome ascertainment. When redeveloping the search, we added terms for cohort studies, included RCTs pre-2019, and focused on *prospective* studies (e.g. removed time series).

Table 2. Eligibility for KQ2 on sequential screening with PSA-based screening plus MRI for biopsy triage versus PSA-based screening alone

	Inclusion criteria	Exclusion criteria
Population	Individuals from the general population not selected for being at increased risk OR Studies may be restricted to those ≥18 years old with an elevated* PSA test after screening (e.g. referred from primary care) sent for biopsy Specific populations of interest for subgroup analyses: • Age: <55 vs. 55 to <70 vs. ≥70 years (KQ1c) • Race or ethnicity (KQ1d) • Family history: none/some (e.g., one second or higher degree relative, unspecified) vs. first-degree/strong history (KQ1d) **definition of elevated to be determined by the included study but must use PSA in ≥80%*	>20% enrolled who were positive on other screening test (e.g. DRE alone) or enrolled after clinical indication/not specified Studies that restrict eligibility to those with specific PSA values (e.g., studies that attempt to limit their eligible population to only those with moderately increased PSA (i.e., not all eligible screeners), or having repeat biopsy
Interventions	Sequential screening i.e., PSA with addition of MRI to determine/triage the need for biopsy In studies only enrolling those with an elevated PSA, MRI before biopsy will be the only intervention Subgroups: Bi-parametric vs. multiparametric MRI; cutoff for the indication of biopsy (PI-RADS ≥3 or ≥4); biopsies using TRUS only vs. MRI guidance vs. other	Any post-biopsy variable/test (e.g., MRI that stratifies risk of an already diagnosed cancer) Use of MRI only to assist biopsy among all with elevated PSA When MRI is used based on a different PSA threshold or criteria than the comparator group
Comparators	Screening with PSA +/- DRE (systematically biopsied after positive screen) Subgroups: TRUS vs. other forms of biopsy (e.g. transperineal); 6-core/sextant vs. 10-12 core TRUS biopsy	Comparisons of no screening will be eligible for KQ1
Outcomes	Potential benefits 1. Reduced prostate cancer mortality 2. Reduced all-cause mortality 3. Reduced incidence of metastatic cancer* Potential harms 4. Positive screen benign for cancer (i.e., false positives = number with benign screen positive / number screened) 5. Complications due to biopsy a. mortality (e.g., 30-day), b. severe AEs (e.g., hematuria, infections), c. serious AEs/hospitalizations, d. all complications 6. Incontinence: a) urinary, b. bowel; binary/risks using patient-report via active ascertainment 7. Erectile dysfunction; binary/risks using patient-report via active ascertainment Either benefit or harm 8. Quality of life or functioning i. generic and ii) disease-specific; composite scores from scales with acceptable measurement properties (e.g., validity, reliability) 9. Psychological effects* Benefit or harm 10. Detection of ii) clinically insignificant cancer (e.g., Gleason 6), and ii) clinically significant cancer* 11. Biopsy referrals* *Outcomes considered important but not critical for decision making.	
Timing of outcome assessment	Benefits: minimum of 5 years after enrollment Outcomes 5-8: any timing and 9: after screening, after positive screening result, after knowledge of benign results, longer term (e.g. ≥6 months) (with similar	

	timepoints in controls); subgroups for 5b-d: ≤30 days post-biopsy vs. longer and for 6-8 short-term (e.g., ≤6 months) vs. longer-term	
Setting	From studies limited to people receiving biopsies, ≥80% recruited from primary care or organized screening program Any country	
Study design	All outcomes: RCTs/quasi-randomized; nonrandomized trials and controlled prospective cohort studies, both with concurrent controls For nonRCTs/cohorts, studies must use design or analysis methods to account for multiple confounders; both methods may be undertaken in same participants (e.g., with blinding to results of comparator) Subgroup analyses: i) contamination/lack of adherence (<25 vs. ≥25% in either arm), ii) high ROB vs. not	
Publication date & type & language	2014-onwards (all studies in a recent systematic review were published after this date) Reports of final study results will be included even if not peer reviewed (e.g., clinical trial registry) Studies with full texts in English or French	Editorials, commentaries, letters, conference proceedings, government reports, narrative reviews, systematic reviews

Note: The scope of this review differs from the previously published protocol in several ways: i) allowing for analysis among a screening population as well as only those with a positive PSA screen, ii) excluding studies where only those with specific PSA values or requiring repeat biopsies are enrolled, iii) limited to interventions adding MRI to triage biopsy among those with positive PSA from screening, iv) removed the outcome of overdiagnosis (limited use when no "no screening" comparator and goal in this KQ is to reduce clinically insignificant cancers) and adding clinically insignificant/significant cancer detection and biopsy referrals as outcomes, v) added specification to other outcome definitions and timing (as per KQ1 but without limit to 2 rounds of screening for Positive screen benign for cancer), vi) added subgroups for intervention and comparator groups and for study design/risk of bias, and vii) limited the publication date to 2014. When redeveloping the search, we added terms for cohort studies, included RCTs published before 2019, and focused on *prospective* studies (e.g. removed time series).

Search strategies

Our information specialist (MT) developed searches in Medline (ALL), Embase (both via OVID platform) and Central (**Appendix**) to capture studies relevant to both KQs. Controlled vocabulary and key words combined concepts for prostate cancer, screening/early detection, and RCTs/controlled trials/prospective cohorts, with a publication date limit of 2014 will be used for the search update. The MEDLINE search was peer reviewed using a standard checklist (PRESS 2015). We will locate RCTs and (for harms) nonrandomized studies for KQ1 published before 2014 from the previous task force review and from other existing systematic reviews (e.g., Ilic et al. 2018, Ilic et al. 2013 (that included RCTs/quasi-RCTs of DRE), USPSTF 2018). We will also hand search ClincialTrials.gov and reference lists of all included studies as well as relevant recent (past 4 years) systematic reviews we locate in our database searches. Results will be imported into EndNote (Clarivate Analytics) and duplicates removed. The searches will be updated within 12 months of the task force guideline being published.

Study selection

We will select records in DistillerSR using a two-stage process, first by title and abstract (screening) and then by full-text (selection). Using standardized forms, all reviewers involved in screening and selection will pilot a random sample of 200 (screening) and 25 records (or 10%, whichever is lower [selection]) prior to each stage. Additional pilot exercises will be conducted until the review team is confident in the application of the criteria and good agreement is reached. After consensus is reached for all records in the pilot screening sample, those decisions as well as other known includes and excludes (published 2014-onwards) from existing systematic reviews will be added to create an initial training set, used to train DistillerSR's AI screening tool. DistillerAI iteratively re-prioritizes records during screening and acts as a proxy reviewer by assigning a likelihood score (0-1, with values closer to 1 indicating higher likelihood of inclusion) based on completed records. Thereafter, two

reviewers will independently screen the first 40-50% of records (or until DistillerAI estimates ≥95% of eligible studies have been located, whichever is greater), after which review by one reviewer will complete the screening (Hamel et al., 2021). Selection will use two independent reviewers with consensus for all articles. If author contact is required to confirm study eligibility, we will email the corresponding author and provide two reminders.

Data extraction, risk of bias assessment, and analysis

Data will be extracted and analyzed to inform both a population perspective (i.e., effects from offering screening) and a patient perspective (i.e., effects from attending screening), and to inform all subgroup analyses (see Tables).

For all outcomes with the exception of quality of life or functioning and psychological effects, data will be extracted as risks (i.e., proportion of people with one or more event) but not rates (i.e., number of events or event rates, time to event). When studies report data for more than one timepoint we will: i) for benefit outcomes use the longest timepoint unless it is higher risk of bias than shorter timepoints, and ii) for other outcomes extract the longest timepoint within each category (e.g., ≤6 and >6 months for health-related quality of life). Data used for subgroup analyses for specific populations (e.g., age groups) will rely on within-study subgroup analysis conducted by study authors, whereas data for other subgroup analyses (e.g., type of MRI or biopsy, risk of bias) may combine within-study data (if interventions differed across participants and effects are reported by these variables) and between-study data. When there are multiple reports used for a study, we will consider the main report used for prostate-cancer mortality as the primary publication (and cite this throughout) but will cite other reports and report in appendices which data is used from each report across outcomes and timepoints. For all nonrandomized studies, we will extract and rely on the most adjusted analysis reported.

All data will be extracted anew. A standard form will be created for data extraction and piloted with at least 2-3 studies per study design, with revisions made to ensure accuracy and completeness. Thereafter, one reviewer will extract and another will verify data for accuracy and completeness, except for results data for KQ1 whereby two reviewers will independently extract data. If author contact is required to seek results data for an outcome or subgroup not reported, we will email the corresponding author and provide two reminders.

Risk of bias assessments will use design-specific tools (e.g., Cochrane ROB2.0 for RCTs) and consider each perspective (see above) separately. Assessments for each outcome and timepoint will be done separately. Apart from risk of bias (for study results) we will also assess risk for missing outcome data, that is, whether there is risk that results have not been reported (or not reported in a usable manner, e.g. only p values) despite data collection by the investigators (as per protocols, trial registry, or published methods). Assessments will be completed by two independent reviewers with consensus, and if necessary third reviewer adjudication, for final decisions.

Analysis will be conducted from both population (e.g., offer to screen regardless of uptake) and patient perspectives (e.g., among attenders), as able. Random effects meta-analysis will be considered when there is sufficient similarity between populations and interventions. Relative risks and mean differences (or standardized mean differences if using data from multiple scales) will be used for comparative studies and proportions will be used for uncontrolled studies (including data of Positive screen benign for cancer and Complications from biopsies among screening groups in comparative studies). Suitable approaches will be used by the statistician (BV) for meta-analysis of rare events and for proportions. These analyses as well as between-study subgroup/stratified analysis will be conducted regardless of statistical heterogeneity. Assessment of heterogeneity and subgroup effects will consider the absolute effects rather than rely only on relative effects. Visual (funnel plots) and statistical tests will be used to asses small-study bias when there are 10 or more studies in an analysis.

Certainty of the evidence

We will assess the certainty of evidence using the most recent guidance from GRADE. Assessments will be guided by choosing targets of the certainty ratings for each outcome, based on thresholds for decision-making (using at least a small-effect threshold for each outcome) that will be developed by the working group before they view any results. For continuous data from patient-reported outcome measures, we will use published minimally-important differences (MIDs) for each scale as the threshold, when available. The assessments will rely on absolute effects which will be calculated using the relative effects of the

studies together with the mean control event rates from the included studies and possibly other assumed rates (e.g., published rate of prostate-cancer death among unscreened population without elevated risk). Assessments will be completed by two independent reviewers with consensus, and if necessary third reviewer adjudication, for final decisions.

Working Group Involvement

The working group determined the outcomes and rated their importance, and made final decisions on the scope of the reviews. They will develop the thresholds of effect for ratings of the certainty of evidence and will help the review team interpret the applicability/directness of the study populations and interventions. They may be involved in study selection for KQ2 when determining whether the population in studies enrolling people attending biopsies represent a screening population; otherwise the review team will make all selection decisions. The working group will not be involved in data extraction, risk of bias assessments, or analyses.

Two patient partners are being recruited by the task force to join the working group. During the conduct of these reviews, they will be involved in determining thresholds for effect when used in the certainty assessments. Thereafter, they will provide input to the working group when making judgements about the magnitude of effects and when interpreting patient preference data as well as information about other factors (e.g., resources, equity considerations) while making their recommendations.

APPENDIX: Search strategies

Ovid MEDLINE(R) ALL

#	Searches
1	exp Prostatic Neoplasms/
2	((prostat* adj3 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or leiomyosarcoma*)) or cspca).tw,kf.
3	1 or 2 [Prostate CA]
4	Mass Screening/
5	screen*.tw,kf.
6	Early Detection of Cancer/
7	"early detection".tw,kf.
8	or/4-7 [Screening]
9	3 and 8 [PCa SCREENING]
10	(controlled clinical trial or randomized controlled trial or pragmatic clinical trial or equivalence trial).pt.
11	"Controlled Clinical Trials as Topic"/
12	exp Randomized Controlled Trials as Topic/
13	(allocat* or randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kf.

14 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf.

15 trial.ti. or trial.ab. /freq=2

16 or/10-15 [RCT]

17 9 and 16 [PCa SCREENING - RCT]

18 controlled clinical trial.pt.

19 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/

20 (control* adj2 trial).tw,kf.

21 Non-Randomized Controlled Trials as Topic/

22 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw,kf.

23 (nRCT or non-RCT).tw,kf.

24 (control* adj2 study).tw,kf.

25 Control Groups/

26 (control* adj2 group?).tw,kf.

27 Cohort studies/

28 (cohort adj (study or studies)).tw,kf.

29 Cohort analys$2.tw,kf.

30 Follow-up studies/

31 Longitudinal studies/

32 Prospective studies/

33 ((Follow-up or followup) adj (study or studies)).tw,kf.

34 Longitudinal.tw,kf.

35 Prospective.tw,kf.

36 (match* or propensity or referent).tw,kf.

37 (discontinuity adj3 (regression or design or study)).tw,kf.

38 "instrumental variable*".tw,kf.

39 "difference in difference".tw,kf.

40 (pilot adj3 study).tw,kf.

41 (or/18-40) not (case-control or retrospective).mp.

42 9 and 41 [PCa SCREENING - nRCT, pilot studies]

43 17 or 42 [PCa SCREENING - RCT, nRCT, pilot studies]

44 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/

45 ((animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.

46 44 or 45 [MUHC Animal filter]

47 43 not 46 [ANIMALS REMOVED]

48 (editorial or news or newspaper article).pt.

49 (letter not (letter and (clinical trial or controlled clinical trial or multicenter study or observational study or randomized controlled trial))).pt.

50 (editorial or commentary).ti.

51 or/48-50

52 47 not 51 [OPINION PIECES REMOVED]

53 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 202*).dt,ez,da.

54 52 and 53 [UPDATE DATE]

55 remove duplicates from 54

Embase

#	Searches
1	prostate tumor/
2	exp prostate cancer/
3	((prostat* adj3 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or leiomyosarcoma*)) or cspca).tw.
4	or/1-3 [Prostate CA]
5	mass screening/
6	cancer screening/
7	screen*.ti,kw. and screen*.ab.
8	screen.ab. /freq=2
9	early cancer diagnosis/
10	"early detection".tw.
11	or/5-10 [SCREENING]
12	4 and 11 [PROSTATE CA - SCREENING]
13	exp randomized controlled trial/ or controlled clinical trial/
14	clinical trial/
15	exp "controlled clinical trial (topic)"/

16 (allocat* or randomi#ed or randomi#ation? or randomly or RCT or placebo*).tw,kw.

17 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw.

18 trial.ti. or trial.ab. /freq=2

19 or/13-18 [RCT FILTER]

20 12 and 19 [PCa SCREENING - RCT]

21 controlled clinical trial/

22 "controlled clinical trial (topic)"/

23 (control* adj2 trial*).tw.

24 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw.

25 (nRCT or non-RCT).tw.

26 controlled study/

27 (control* adj2 study).tw.

28 (control* adj2 group?).tw.

29 (cohort adj (study or studies)).tw.

30 cohort analysis/

31 Cohort analys$2.tw.

32 follow up/

33 longitudinal study/

34 prospective study/

35 ((Follow-up or followup) adj (study or studies)).tw.

36 Longitudinal.tw.

37 Prospective.tw.

38 (match* or propensity or referent).tw.

39 (discontinuity adj3 (regression or design or study)).tw.

40 "instrumental variable*".tw.

41 "difference in difference".tw.

42 (pilot adj3 study).tw.

43 (or/21-42) not (case-control or retrospective).mp. [non-RCT]

44 12 and 43 [PROSTATE CA - SCREENING - non-RCT]

45 20 or 44 [PCa SCREENING - RCT, nRCT, pilot studies]

46 exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/

47 exp human/ or exp human experimentation/ or exp human experiment/

48 46 not 47

49 ((animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not human*).mp.

50 48 or 49

51 45 not 50 [ANIMALS REMOVED]

52 (conference abstract or editorial).pt.

53 letter.pt. not (letter.pt. and (clinical trial/ or controlled clinical trial/ or multicenter study/ or randomized controlled trial/))

54 (editorial or commentary).ti.

55 52 or 53 or 54

56 51 not 55 [CONF ABS, OPINION PIECES REMOVED]

57 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 202*).dc.

58 56 and 57 [UPDATE DATE]

59 remove duplicates from 58

CENTRAL

ID	Search	Hits
#1	[mh "Prostatic Neoplasms"]	9094
#2	((prostat* NEAR/2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or leiomyosarcoma*)) or cspca):ti,ab,kw	18633
#3	#1 OR #2	18633
#4	[mh ^"Mass Screening"]	5206
#5	screen*:ti,ab,kw	109762
#6	[mh ^"Early Detection of Cancer"]	2684
#7	"early detection":ti,ab,kw	5867
#8	#4 OR #5 OR #6 OR #7	112121
#9	#3 AND #8 with Publication Year from 2014 to 2024, in Trials	1325