Special Assessment to Inform CMS Drug Price Negotiations: Darolutamide (Nubeqa®) for Patients with Prostate Cancer

Research Protocol

September 10, 2026

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1. Background, Objectives, and Research Questions

1.1. Background

ICER previously reviewed Antiandrogen Therapies for Prostate Cancer.[1] Much of the information in this background section is updated from that report, with the addition of new information gained from updated literature review and scoping calls with experts.

Prostate cancer is the second most common cause of cancer death in American men (after lung cancer), and the most common cancer in men other than non-melanoma skin cancers.[2] It is estimated that there will be approximately 333,830 new cases of prostate cancer and 36,320 prostate cancer deaths in the United States (US) in 2026.[2] Prostate cancer disproportionately affects black men, with an incidence that is approximately 67% higher and a mortality rate that is double that of white men.[3] Older studies estimate that the annual direct medical costs for prostate cancer in the US are approximately $15 billion, and indirect costs are approximately $5.4 billion.[4,5]

Prostate cancer typically responds to androgen deprivation therapy (ADT).[6] ADT involves medical or surgical castration. Medications used for ADT include gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide, goserelin, and triptorelin,[7] and GnRH antagonists, such as degarelix.[8]

ADT is used in a number of clinical settings, including disseminated prostate cancer, high-risk prostate cancer treated with radiation therapy, and prostate cancer treated with radical prostatectomy found to have positive pelvic lymph nodes.[9] Prostate cancer that has not been treated with ADT or that is responding to ADT is called castration-sensitive prostate cancer (CSPC). Over time, most cancers that were castration sensitive become castration resistant. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved low levels of serum testosterone.[9] In recent years, new terms have been introduced to describe treatment response. For example, the Prostate Cancer Clinical Trial Working Group 4 recommends the terms "androgen pathway modulation naïve or sensitive prostate cancer" for CSPC and "androgen pathway modulation resistant" for CRPC.[10] However, these terms have not yet been incorporated into clinical guidelines or adopted broadly, nor were they used by CMS during the negotiation process for enzalutamide last year. Thus, we have elected to retain the traditional terms while acknowledging that many patients find the language to be harsh and dehumanizing.

Antiandrogen therapies play a significant role in the treatment of metastatic CSPC (patients with metastatic disease who are still responsive to ADT) and metastatic CRPC (patients with metastatic disease who continue to progress on ADT). Similarly, patients without metastatic disease who progress on ADT with a prostate-specific antigen (PSA) doubling time of less than or equal to 10 months (non-metastatic castration-resistant prostate cancer; nmCRPC) benefit from treatment with antiandrogen therapies.

The second-generation antiandrogens are newer and are currently more commonly used in clinical practice. These include abiraterone acetate (Zytiga®; Janssen Biotech, Inc.), enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer), apalutamide (Erleada®; Janssen Biotech, Inc.), and darolutamide (Nubeqa®, Bayer). Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues; abiraterone acetate must be administered with corticosteroids (typically prednisone).[6,11] Enzalutamide, apalutamide, and darolutamide are androgen receptor inhibitors that bind to the ligand-binding domain of the androgen receptor.[6,11]

1.2. Objectives

This project will assess both the comparative clinical effectiveness and economic impacts of the newest of the second-generation antiandrogen therapies – darolutamide – for the treatment of prostate cancer. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan (expected posting: 10/27/2026) for details on the proposed methodology and model structure to be used in the economic evaluation.

1.3. Research Questions

To inform our review of the clinical evidence, we have developed the following research questions:

Research Questions for nmCRPC:

1. What is the net health benefit of darolutamide versus apalutamide in patients with nmCRPC?
2. What is the net health benefit of darolutamide versus enzalutamide in patients with nmCRPC?

Research Questions for mCSPC:

3. What is the net health benefit of darolutamide versus apalutamide in patients with mCSPC?
4. What is the net health benefit of darolutamide plus docetaxel versus apalutamide plus docetaxel in patients with mCSPC?
5. What is the net health benefit of darolutamide versus enzalutamide in patients with mCSPC?
6. What is the net health benefit of darolutamide plus docetaxel versus enzalutamide plus docetaxel in patients with mCSPC?
7. What is the net health benefit of darolutamide versus abiraterone acetate in patients with mCSPC?
8. What is the net health benefit of darolutamide plus docetaxel versus abiraterone acetate plus docetaxel in patients with mCSPC?

1.4. PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Populations

The population of focus for the review is based on the approved indications for darolutamide, which are:

- Population 1: men with non-metastatic castration-resistant prostate cancer (nmCRPC) with a PSA doubling time of ≤10 months
- Population 2: men with metastatic castration-sensitive prostate cancer (mCSPC)

Data permitting, we will evaluate evidence on effectiveness and harms within subpopulations defined by:

- Demographic factors (e.g., age, race, ethnicity)
- Metastatic disease volume (high versus low)
- Eastern Cooperative Oncology Group (ECOG) score

Interventions

The intervention of interest for this review is:

- Population 1
    - Darolutamide (Nubeqa®, Bayer)
- Population 2:
    - Darolutamide with or without docetaxel

Comparators

Data permitting, we intend to compare to:

- Population 1:
    - Apalutamide (Erleada®, Janssen Biotech Inc.)
    - Enzalutamide (Xtandi®, Astellas Pharma and Pfizer)
- Population 2: We will evaluate the following interventions with and without docetaxel
    - Apalutamide (Erleada®, Janssen Biotech Inc.)
    - Enzalutamide (Xtandi®, Astellas Pharma and Pfizer)
    - Abiraterone acetate

All patients receiving the intervention or comparator will be expected to be treated with androgen deprivation therapy (ADT).

Outcomes

The outcomes of interest are listed below.

- Patient-Important Outcomes
    - Overall survival
    - Progression-free survival
    - Fatigue
    - Health-related quality of life
    - Grade ≥3 adverse events
- Other Outcomes
    - Metastasis-free survival
    - Symptomatic progression
    - PSA progression
    - Discontinuation due to adverse events
    - Adverse events including

- Cardiovascular events
- Central nervous system-related AEs (e.g., cognitive impairment, seizures, falls)
- Fracture
- Fluid retention
- Hypertension
- Hypokalemia
- Hypothyroidism
- Rash

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Study Design

Randomized controlled trials with any sample size will be included. High-quality comparative observational studies will also be included that have a sample size greater than 500 and a duration longer than 18 months.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on darolutamide for prostate cancer will follow established best methods.[12,13] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

To address our eight research questions, we are primarily interested in understanding whether there are differences in efficacy and safety between darolutamide and the comparators. In the absence of head-to-head studies of darolutamide versus the comparators, we will perform indirect comparisons between darolutamide and the comparators for patients with both nmCRPC and mCSPC. Our search strategy will be separated into two sections: randomized controlled trials (RCTs) and observational studies.

For the RCT search, we identified two recent systematic reviews and network meta-analyses of darolutamide and other antiandrogens, one for each population of interest, which followed a similar scope to the one planned for this review to update.[15,16] We will identify RCTs of darolutamide and comparators that meet our criteria from these systematic reviews, and then search for new evidence by conducting an updated literature review. We will search MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials for additional RCTs published from 2020, overlapping with the earliest search date among the two identified systematic reviews.

For observational studies, we will conduct a de novo search of MEDLINE and EMBASE to identify studies evaluating darolutamide.

Each search will be limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 2.1. and 2.2. below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and other systematic literature reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published

studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

Table 2.1. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Clinical Trials Only)

#	Search Terms
1	exp prostatic neoplasms/
2	("Non-metastatic castration-resistant prostate cancer" OR "nmCRPC" OR "non-metastatic hormone-resistant prostate cancer" OR "nmHRPC" OR "metastatic castration-sensitive prostate cancer" OR "mCSPC" OR "metastatic hormone-sensitive prostate cancer" OR "mHSPC").ti,ab.
3	1 OR 2
4	("bay 1841788" OR "bay1841788" OR "darolutamide" OR "Nubeqa" OR "ODM-201" OR "ORM-16497" OR "ORM-16555").ti,ab.
5	("apalutamide" OR "arn 509" OR "ARN-509" OR "arn509" OR "Erleada" OR "jnj 56021927" OR "jnj 927").ti,ab.
6	("enzalutamide" OR "enzalutamide D3" OR "HC 1119" OR "HC-1119" OR "mdv 3100" OR "MDV-3100" OR "mdv3100" OR "xtandi").ti,ab.
7	("abiraterone acetate" OR "abretone" OR "bixodalan" OR "cb 7630" OR "CB-7630" OR "cb7630" OR "drgt 45" OR "drgt45" OR "grumabix" OR "jnj 212082" OR "jnj212082" OR "remabirat" OR "sol 804" OR "sol804" OR "tatica" OR "tavt 45" OR "tavt45" OR "yonsa" OR "zaitiga" OR "zaytiga" OR "zitiga" OR "zytiga").ti,ab.
8	4 or 5 or 6 or 7
9	3 and 8
10	9 not (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt.
11	10 NOT (animals not (humans and animals)).sh.
12	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv" or "controlled clinical trial" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
13	exp cohort studies/ or exp case control studies/ or retrospective.ti,ab. or "case series".ti,ab. or "case control study".ti,ab. or "cohort study".ti,ab.
14	11 and 12
15	14 not 13
16	Remove duplicates from 15
17	Limit 16 to English language
18	Limit 17 to yr="2020-current"

Table 2.2. Search Strategy of EMBASE SEARCH (Clinical Trials Only)

#	Search Terms
1	'prostate cancer'/exp
2	('Non-metastatic castration-resistant prostate cancer' OR 'nmCRPC' OR 'non-metastatic hormone-resistant prostate cancer' OR 'nmHRPC' OR 'metastatic castration-sensitive prostate cancer' OR 'mCSPC' OR 'metastatic hormone-sensitive prostate cancer' OR 'mHSPC'):ti,ab
3	#1 OR #2
4	('bay 1841788' OR 'bay1841788' OR 'darolutamide' OR 'Nubeqa' OR 'ODM-201' OR 'ORM-16497' OR 'ORM-16555'):ti,ab
5	('apalutamide' OR 'arn 509' OR 'ARN-509' OR 'arn509' OR 'Erleada' OR 'jnj 56021927' OR 'jnj 927'):ti,ab
6	('enzalutamide' OR 'enzalutamide D3' OR 'HC 1119' OR 'HC-1119' OR 'mdv 3100' OR 'MDV-3100' OR 'mdv3100' OR 'xtandi'):ti,ab
7	('abiraterone acetate' OR 'abretone' OR 'bixodalan' OR 'cb 7630' OR 'CB-7630' OR 'cb7630' OR 'drgt 45' OR 'drgt45' OR 'grumabix' OR 'jnj 212082' OR 'jnj212082' OR 'remabirat' OR 'sol 804' OR 'sol804' OR 'tatica' OR 'tavt 45' OR 'tavt45' OR 'yonsa' OR 'zaitiga' OR 'zaytiga' OR 'zitiga' OR 'zytiga'):ti,ab
8	#4 OR #5 OR #6 OR #7
9	#3 AND #8
10	#9 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
11	#10 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
12	'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab OR 'randomised controlled trial':ti,ab OR randomi?ed:ti,ab OR randomly:ti,ab OR placebo:ti,ab OR 'double blind':ti,ab OR 'double-blind':ti,ab OR 'single blind':ti,ab OR 'crossover procedure'/exp
13	'case control study'/exp OR 'cohort analysis'/exp OR 'retrospective study'/exp OR 'observational study'/exp
14	#11 AND #12
15	#14 NOT #13
16	#15 NOT [medline]/lim
17	#16 AND [english]/lim
18	#17 AND [2020-current]/py

Table 2.3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials (Observational Studies Only)

#	Search Terms
1	exp prostatic neoplasms/
2	("non-metastatic castration-resistant prostate cancer" or "nmCRPC" or "non-metastatic hormone-resistant prostate cancer" or "nmHRPC" or "metastatic castration-sensitive prostate cancer" or "mCSPC" or "metastatic hormone-sensitive prostate cancer" or "mHSPC").ti,ab.
3	1 OR 2
4	("bay 1841788" OR "bay1841788" OR "darolutamide" OR "Nubeqa" OR "ODM-201" OR "ORM-16497" OR "ORM-16555").ti,ab.
5	3 and 4
6	5 not (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or

	newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt.
7	6 NOT (animals not (humans and animals)).sh.
8	exp cohort studies/ or observational study.pt. or exp case-control studies/ or exp cross-sectional studies/ or cohort.tw. or (observational adj2 stud*).tw. or prospective.tw. or retrospective.tw. or longitudinal.tw. or "case control".tw. or "case-control".tw. or multivariate.tw.
9	randomized controlled trial.pt. or controlled clinical trial.pt. or randomi?ed.ti,ab. or placebo.ti,ab. or ((single or doubl*) adj2 blind*).ti,ab. or crossover procedure/
10	7 and 8
11	10 not 9
12	Remove duplicates from 11
13	Limit 12 to English language

Table 2.4. Search Strategy of EMBASE SEARCH (Observational Studies Only)

#	Search Terms
1	'prostate cancer'/exp
2	(‘Non-metastatic castration-resistant prostate cancer’ OR ‘nmCRPC’ OR ‘non-metastatic hormone-resistant prostate cancer’ OR ‘nmHRPC’ OR ‘metastatic castration-sensitive prostate cancer’ OR ‘mCSPC’ OR ‘metastatic hormone-sensitive prostate cancer’ OR ‘mHSPC’):ti,ab
3	#1 OR #2
4	('bay 1841788' OR 'bay1841788' OR 'darolutamide' OR 'Nubeqa' OR 'ODM-201' OR 'ORM-16497' OR 'ORM-16555'):ti,ab
5	#3 and #4
6	#5 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
7	#6 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)
8	'observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'case control study'/exp OR 'cross-sectional study'/exp OR 'case series'/exp OR cohort:ti,ab OR 'case control':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab)
9	'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab OR 'randomised controlled trial':ti,ab OR randomi?ed:ti,ab OR placebo:ti,ab OR 'double blind':ti,ab OR 'crossover procedure'/exp
10	#7 AND #8
11	#10 NOT #9
12	#11 NOT [medline]/lim
13	#12 AND [english]/lim

2.2. Study Selection Process

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using Nested Knowledge; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at

abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

2.3. Data Extraction Strategy

Data will be extracted into Microsoft Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.

2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

As part of an AI pilot, we will use Claude for data extraction for a few studies. For these studies, there will be human oversight for table shell generation and data validation.

2.4. Risk of Bias

We will examine the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[17,18] Where relevant, we will examine the risk of bias for observational studies. Risk of bias will be assessed for each study outcome across the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers will independently assess these domains. Any disagreements will be resolved through discussion or by consulting a third reviewer.

2.5. Subgroup Credibility

We will examine the credibility of subgroup analyses (aka effect modification analyses) determined to be clinically important for the review using criteria published in the Instrument for the Credibility of Effect Modification Analyses (ICEMAN) tool (Version 1.1).[19] The credibility of each effect modifier

will be assessed by outcome of interest, time point of interest, and effect measure. One reviewer will independently assess the credibility of the subgroup analyses, and a second reviewer will validate the ratings.

2.6. Clinical Trial Diversity

We will evaluate the demographic diversity for each clinical trial in this review using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[20] Three demographic categories will be evaluated: race and ethnicity, sex, and age. Representation for each demographic category will be evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Each article will receive a rating of "Good", "Fair", or "Poor" for the three demographic categories. One reviewer will use the extracted and validated trial data to calculate the ratings. A second reviewer will validate the ratings.

2.7. Publication Bias

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "darolutamide" and "prostate cancer". We will select studies that would have met our inclusion criteria and for which no findings have been published. We will provide a qualitative analysis of the objectives and methods of these studies to ascertain whether there is a biased representation of study results in the published literature.

2.8. Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains a summary of the evidence base and synthesis of outcome results.

Summary of the Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and assessment methods), and study quality will be noted in the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

We also will assess the feasibility of conducting a network meta-analysis (NMA) under a Bayesian framework. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[21,22] For outcomes such as time to event data (e.g., number of deaths and treatment exposure time in person-years), the NMA model corresponds to a generalized linear model with a log link (Poisson distribution). For continuous outcomes (e.g., relative estimate of overall survival), the NMA model corresponds to a generalized linear model with identity link. For binary outcomes (e.g., discontinuation due to adverse events), the NMA model corresponds to a generalized linear model with a logit link. For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons. We will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using three chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run sequentially until convergence.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[23] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

All NMAs will be conducted using RStudio and/or IndiRect NMA platform (CRG-EVERSANA, 2020™). Results for all comparisons will be presented with point estimates and 95% credible intervals. We will also present results graphically for each intervention versus listed comparators listed above.

All data analysis will be validated by an independent member of the research team. The validator will review and confirm the data analysis methods, data format, and analysis code. The validator will re-run the analysis, validate the results, and confirm the appropriateness of reported data. If the results match within reasonable limits (e.g., small differences may occur due to random sampling variability or model convergence, package versions, etc.), the results are considered validated.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Page et al. 2021.[14]

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.

	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.

	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Appendix B. Data Extraction Summary Table Shell

Table B1. Study Design

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Comparator (s)	Inclusion & Exclusion Criteria	Primary Endpoint	Follow-Up
Trial A						
Trial B						
Trial C						

N: number

Table B2. Baseline Characteristics

Trial		Trial A		Trial B		Trial C	
Arm							
N							
Age, Mean (SD) or Median							
Time from Initial Diagnosis, Months							
Presence of Lymph Nodes, n(%)	**Yes**						
	No						
PSA Level, ng/ml							
PSA Doubling Time, Months	**Median**						
	≤6 Months						
	>6 Months						
Median Serum Testosterone, nmol/liter							
ECOG Performance Status, n(%)	**0**						
	1						
Previous Hormonal Therapy, n(%)	**1**						
	2+						
Use of Bone Sparing Agent, n(%)	**Yes**						
	No						
And More…							

ECOG: Eastern Cooperative Oncology Group, ml: milliliters, ng: nanograms, N: number, PSA: prostate-specific antigen, SD: standard deviation

Table B3. Efficacy

Trial		Trial A		Trial B		Trial C	
Arm							
N							
MFS	**Median (Months)**						
	No of Events						
OS	**Median (Months)**						
	No of Events						
PFS	**Median (Months)**						
	No of Events						
Time to PSA Progression	**Median (Months)**						
	No of Events						
And More…							

MFS: metastasis-free survival, N: number, OS: overall survival, PFS: progression-free survival, PSA: prostate-specific antigen

Table B4. Safety

Trial		Trial A		Trial B		Trial C	
Arm							
N							
Discontinuations, n(%).							
Discontinuations due to AEs, n(%)	**Overall**						
	Grade 3/4						
AEs, n(%)	**Overall**						
	Grade 3/4						
SAEs, n(%)	**Overall**						
	Grade 3/4						
And More…							

AE: adverse event, n: number, SAE: serious adverse event