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Enzalutamide (XTANDI™) for the treatment of adult men with asymptomatic or mildly symptomatic metastatic hormone relapsed prostate cancer after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated

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List of abbreviations

Abbreviation	Definition
≥50%	≥50% decline in PSA levels
≥90%	≥90% decline in PSA levels
ABI	Abiraterone
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
AE	Adverse event
AF	Acceleration Factors
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ASCO-GU	American Society of Clinical Oncology- Genitourinary
AST	Aspartate aminotransferase
BD	Twice daily
BIC	Bayesian Information Criterion
BNF	British National Formulary
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
BSC	Best Supportive Care
CEAC	Cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CR	Complete response
CrI	Credible interval
CSR	Clinical Study Report
CT	Computed Tomography
CYP	Cytochrome P450
DB	Double blind
DHT	Dihydrotestosterone
DMC	Data monitoring committee
DSU	Decision support unit
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
ENZA	Enzalutamide
EQ-5D	European quality of life five-domain scale
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EWB	Emotional Wellbeing
FACT-G	Functional Assessment Of Cancer Therapy – General
FACT-P	Functional Assessment Of Cancer Therapy – Prostate
FDA	Food and Drug Administration

Abbreviation	Definition
FWB	Functional Wellbeing
G-CSF	Granulocyte colony-stimulating factor
GnRH	Gonadotropin releasing hormone
HR	Hazard Ratio
HRG	Healthcare resource group
HRPC	Hormone-relapsed prostate cancer
HRQL	Health Related Quality of Life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IPCW	Inverse Probability of Censoring Weights
IPE	Iterative Parameter Estimation
ITC	Indirect treatment comparison
ITT	Intention To Treat
IVRS	Interactive voice and web response services
KM or K-M	Kaplan Meier
LDH	Lactate Dehydrogenase
LH	Luteinising Hormone
LHRH	Luteinising Hormone-Releasing Hormone
LS mean	Least Squared mean
LYG	Life years gained
Mcg	Microgram
MCID	Minimal clinically important difference
Mg	Milligram
mHRPC	Metastatic hormone-relapsed prostate cancer
MMRM	Mixed Models with Repeated Measures
MRI	Magnetic Resonance Imaging
NA	Not applicable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NR	Not reported
NYR	Not yet reached
OD	Once daily
OLS	Ordinary least squares
OR	Odds ratio
OS	Overall Survival
OWSA	One way sensitivity analysis
PAP-GM-CSF	Prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor
PAS	Patient Access Scheme
PCS	Prostate Cancer Scale
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PFS	Progression Free Survival
PH	Proportional hazards
PLA	Placebo
PO	Per os (oral)
PP1	Post-progression 1

Abbreviation	Definition
PP2	Post-progression 2
PR	Partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PRED	Prednisone
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSA	Prostate Specific Antigen
PSSRU	Personal Social Services Research Unit
Pts	Patients
PWB	Physical Wellbeing
QoL	Quality of Life
RCT	Randomised Clinical Trial
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	Radiographic Progression-Free Survival
RPSFTM	Rank Preserving Structural Failure Time Model
RR	Relative risk
SA	Sensitivity analysis
SAE	Serious adverse event
SDis	Stable disease
SE	Standard error
SPC	Summary of product characteristics
SRE	Skeletal-related event
STA	Single technology appraisal
SWB	Social wellbeing
SWi	Stabilised weights
TTD	Time to Treatment Discontinuation
UK	United Kingdom
VAS	Visual Analogue Scale
Wk	Week
WKM	Weighted Kaplan Meier
WTP	Willingness to pay
Yrs	Years

List of definitions

Term	Definition
HRPC	Hormone-relapsed prostate cancer (HRPC) is defined by the 2014 EAU Guideline on prostate cancer as having: • Castrate serum levels of testosterone (testosterone <50 ng/dl or <1.7 nmol/l), plus either: - Biochemical progression defined as three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA >2 ng/mL, OR - Radiological progression defined as the appearance of two or more bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in solid tumours). PREVAIL recruited patients with metastatic HRPC (mHRPC). In this respect, HRPC is the equivalent to castration-resistant prostate cancer (CRPC). In this document, CRPC is referred to as HRPC. In PREVAIL, patients had to meet the following criteria to be randomised: • Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features. • Ongoing ADT with a GnRH analogue or orchiectomy (i.e., surgical or medical castration). • For patients who have not had an orchiectomy, there must be a plan to maintain effective GnRH-analogue therapy for the duration of the trial. • Serum testosterone level <1.7 nmol/L (50 ng/dL) at the Screening visit. • Progressive disease by PSA or imaging after docetaxel-based chemotherapy in the setting of medical or surgical castration. Disease progression for study entry was defined as PSA progression, Soft tissue disease progression according to RECIST or Bone disease progression defined by two or more new lesions on bone scan.
Data analyses for PREVAIL	The study was stopped by an independent Ethics Committee after a planned interim analysis at 516 deaths (here-in referred to as the *16th September 2013 data cut*) and was then unblinded on the 3rd December 2013, (here-in referred to as the *3rd December 2013 data cut*). The study was considered to have ended following unblinding, however patients continued to be followed-up to monitor safety at the request of the FDA. Patients on placebo were offered treatment with enzalutamide following unblinding. In January 2014 an additional analysis was conducted as part of the 90-day safety submission to the FDA. An analysis of OS was conducted as part of this FDA submission (here-in referred to as the *January 2014 data cut*). The results of this analysis were published in the Appendix of Beer et al. For simplicity, the results of this data cut-off are not included in this submission. Upon granting approval for the additional indication of enzalutamide, the FDA requested an additional analysis for OS be conducted at around the protocol led number of 765 deaths (i.e. in line with the pre-specified final analysis if the trial had not already been unblinded). An event sweep was conducted to ensure the survival status of patients and their follow-up while in the trial were fully captured. The cut-off date for this analysis was 1st June 2014 (here-in referred to as the *1st June 2014 data cut*), however the event sweep delayed the availability of these results for inclusion in the survival and health economic modelling detailed in this submission. As such, a further analysis was performed on 30 June 2014 to ensure that the most mature data was used for modelling purposes (here-in referred to as the *30th June 2014 data cut*) . No event sweep was conducted for this

	data cut. The overall survival results presented in this document relate to the 16 September 2013 and 30 June 2014 data cuts. The different data cut-offs conducted for the co-primary PREVAIL endpoints are summarised below. <table><tr><th></th><th>OS</th><th>rPFS</th></tr><tr><td>Pre-planned</td><td></td><td></td></tr><tr><td>Interim</td><td>*Planned* at approx 516 deaths • *Data cut-off*: 16 September 2013 (540 events; median FU: 22.2 and 22.4 months)</td><td>Not applicable</td></tr><tr><td>Final</td><td>*Planned at* 765 deaths • 1 June 2014 (results not yet available)</td><td>*Planned at* 410 centrally reviewed events • *Data cut-off: 06 May 2012 (439 events; median FU: 5.4 and 3.6 months)* *Sensitivity analysis* for investigator assessed PFS • *Data cut-off: 16 Sept 2013 (889 events; median FU: 22.2 and 22.4 months)*</td></tr><tr><td>Post-hoc</td><td>*Two data cut-offs:* • 15 January 2014 (665 events; median FU: 26.2 and 26.5 months) • 30 June 2014 – for modelling purposes (775 events)</td><td></td></tr></table>
mHRPC	Metastatic hormone-relapsed prostate cancer is defined as HRPC with known metastases.
OS	Time from randomisation to death of any cause.
Pain progression	Pain progression was assessed using the worst pain (item #3 of the BPI), the pain severity composite score and the pain interference composite score.
PSA response	PSA response is defined as ≥50% and ≥90% reductions in PSA from baseline to the lowest post-baseline PSA result.
PSA progression	PSA progression was defined according to the consensus guidelines of the PCWG2 as: • ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir, with confirmation by a second consecutive value obtained ≥ 3 weeks later. • For patients with no PSA decline at Week 13, PSA progression was defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above baseline was documented, which was confirmed by a second consecutive value 3 or more weeks later.
HRQL response	The HRQL improvement was defined as an MCID-point or higher improvement in a HRQL score at a post-baseline assessment as compared to baseline assessment. The upper bound of the MCID range corresponding to each instrument was used
Radiographic response	Radiographic response was assessed according to the RECIST version 1.1 for soft tissue disease.
rPFS	Time from randomisation date to radiological progression according to RECIST version 1.1 for soft tissue disease and to PCWG2 criteria for bone

	progression
SRE	The definition of a skeletal-related event can vary across studies. In the context of PREVAIL, a skeletal related event (SRE) is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An alteration of analgesic medication for bone pain or the initiation of bisphosphonates or denosumab was not considered a SRE.
TTD	Time from first dose to treatment discontinuation.
Chemotherapy	Chemotherapy refers to cytotoxic chemotherapy.

Executive summary

Introduction

- Enzalutamide (XTANDI™) is a new treatment for adult men with metastatic hormone-relapsed prostate cancer (mHRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated[1]. This submission compares enzalutamide with the current standards of care in this indication (here-in referred to as the chemo-naïve setting): abiraterone and best supportive care (BSC).
- Until recently, treatment of mHRPC was limited to BSC followed by chemotherapy with docetaxel when patients become symptomatic. Recently there have been new developments in this area and abiraterone is available for the chemo-naïve setting. While still under review with NICE, already an estimated 53% of patients are receiving abiraterone for this indication through the Cancer Drug Fund (CDF) which indicates the high unmet need in this patient population. Abiraterone is the principal comparator in this submission.
- This submission demonstrates cost-effectiveness versus both comparators (abiraterone and BSC).
- Evidence of the efficacy and safety of enzalutamide in the chemo-naïve setting originates from the PREVAIL trial, a large international randomised, placebo-controlled double-blind study comparing enzalutamide to placebo[2,3]. In the study, enzalutamide met all the co-primary and secondary endpoints. PREVAIL demonstrated statistically significantly higher overall survival (OS) and radiographic progression-free survival (rPFS) for enzalutamide over BSC while maintaining patient's health related quality of life (HRQL).
- This dossier is a resubmission at the request of NICE using list prices for enzalutamide and abiraterone in place of the existing Patient Access Scheme prices.

Regulatory and reimbursement information

- On 21 June 2013, XTANDI was approved by the European Medicines Agency (EMA) for the treatment of adult men with mHRPC whose disease has progressed on or after docetaxel therapy (here-in referred to as the post-chemo setting).
- Enzalutamide has been available in the UK for the chemo-naive indication since receiving the marketing authorisation in November 2014.
- Enzalutamide (160 mg) should be administered orally, once a day, in the form of four 40 mg capsules. Enzalutamide offers the flexibility to be prescribed with or without concomitant steroids, requires less routine monitoring for liver toxicity, hypokalaemia, fluid overload, and blood pressure than abiraterone, and can be administered with or without food1.

In the chemo naive setting, enzalutamide will have a PAS discount of [redacted] as per the existing PAS in the post chemo setting. However, the full list price has been used in the economic base case at the request of NICE.

Mode of Action

- Enzalutamide is an oral androgen receptor (AR) signalling inhibitor which acts at three distinct levels of the signalling pathway: 1) it completely inhibits binding of androgens to ARs in the interior of prostate cells (cytosol); 2) it inhibits the nuclear translocation of activated receptors; 3) it inhibits the association of the activated AR with DNA. Enzalutamide demonstrates this activity even when AR is over-expressed in the prostate cancer cells resistant to anti-androgens1. Unlike AR antagonists that can act as partial agonists, enzalutamide is a pure AR antagonist.

- The mechanism of action of enzalutamide is different from the current standard of care – abiraterone which irreversibly blocks cytochrome P17 (an enzyme involved in the production of testosterone), thereby stopping androgen synthesis in the adrenal glands, testes and the prostatic tumour[4]. The mechanism of action of abiraterone is associated with side effects which require management via administration of concomitant steroids, which necessitates some additional monitoring.

Clinical Evidence

- Evidence of the efficacy of enzalutamide (160 mg) in the chemo-naïve setting originates from PREVAIL, a large randomised double-blind placebo-controlled phase III study (1,717 patients)3. In PREVAIL patients were randomised (1:1 ratio) to either enzalutamide or placebo, both in addition to BSC. Both treatment arms were well balanced for demographics and baseline characteristics. Overall, 53.1% of patients in PREVAIL were recruited in Europe and 8.9% (N=153/1,717) in the UK (12 sites).
- All primary and secondary endpoints were met with enzalutamide whilst being well tolerated.
- The intention-to-treat (ITT) patient population from PREVAIL has been used to inform this submission, and demonstrates that enzalutamide is a highly effective treatment:
    - ◊ Significantly lower risk of death compared with placebo (unstratified HR: 0.706; 95% CI: [0.596, 0.837]; p<0.0001) in the protocol pre-specified interim analysis (16 September 2013) after 241 and 299 deaths in the enzalutamide and placebo arm, respectively. Median overall survival (OS) was 32.4 months (95% CI: [30.1; not yet reached]) with enzalutamide vs 30.2 months (95% CI: [28.0; not yet reached]) with placebo.
    - ◊ Significantly lower risk of death (unstratified HR: [redacted] p<0.001) in the 30 June 2014 cut-off conducted for modelling purposes. After [redacted] and [redacted] deaths in the enzalutamide and placebo arms, respectively median OS was [redacted] months with enzalutamide and [redacted] months with placebo.
    - ◊ Significantly lower risk of radiographic disease progression at the protocol pre-specified final analysis at 439 centrally-assessed events. In this analysis, median rPFS had not yet been reached for enzalutamide (HR: 0.186, 95% CI [0.149; 0.231]; p<0.0001).
    - ◊ Significantly lower risk in radiographic disease progression as assessed by the investigator (HR: 0.307, 95% CI [0.267; 0.353]). Radiographic PFS as assessed by the investigator was a preplanned sensitivity analysis. The data cut-off for this analysis was 16 September 2013. Median rPFS after 889 investigator-assessed events was 19.7 months and 5.4 months in the enzalutamide and placebo arms, respectively.
    - ◊ Significantly lower risk of experiencing a first skeletal-related event (SRE; HR: 0.718 95% CI: [0.610, 0.844], p < 0.0001). Median time to first SRE was 31.1 months (95% CI: [29.5, not yet reached]) with enzalutamide vs 31.3 months (95% CI [23.9, not yet reached]) with placebo
    - ◊ Significantly lower risk of initiation of cytotoxic chemotherapy (HR: 0.349, 95% CI [0.303; 0.403], p<0.0001). Median time to initiation of cytotoxic chemotherapy was 28.0 months (95% CI [25.8; not yet reached]) with enzalutamide and 10.8 months (95% CI [9.7; 12.2]) with placebo
    - ◊ Significantly lower risk of PSA progression (HR: 0.169, 95% CI [0.147, 0.195], p<0.0001). Median time to PSA progression was 11.2 months (95%

CI [11.1, 13.7]) with enzalutamide and 2.8 months (95% CI [2.8, 2.9]) with placebo.

  - ◊ Significantly lower risk to average pain progression as measured by the brief pain inventory (BPI; HR: 0.60, 95%CI: [0.51;0.71]; p<0.001). Median time to pain progression was 5.65 months (95% CI, [5.59; 5.68]) with enzalutamide and 5.55 months (95% CI [3.09; 5.55]) with placebo
  - ◊ Significantly lower risk of HRQL deterioration than placebo as assessed with FACT-P (HR: 0.62, 95% CI: [95% CI: 0.54; 0.72]; p<0.001) or EQ-5D (HR: 0.62 (95%CI: [0.52; 0.73]; p<0.001). Median time to HRQL deterioration was 11.30 months vs 5.55 months with FACT-P and 19.19 months vs 11.07 months with EQ-5D

- PREVAIL also demonstrated that enzalutamide is a well tolerated treatment:
  - ◊ The overall incidence of adverse events (AEs) was similar for enzalutamide and placebo despite the markedly longer exposure to study drug in the enzalutamide arm. Serious and grade 3+ AEs tended to be more common in the enzalutamide arm in the overall analysis period but were more frequently observed in the placebo arm during the first 12 months.
- In PREVAIL, patients who discontinued study treatment in either arm could receive a new active treatment. In the most mature data cut-off (30 June 2014) [redacted] and [redacted] of patients in the enzalutamide and placebo arm, respectively received an active agent after treatment discontinuation (i.e., as 2nd line treatment) which differed from the treatment patients would have received in real UK clinical practice and with the potential to influence OS; these patients are hereafter referred to as switchers. Switching could bias estimates of the true OS benefit of enzalutamide. When patients switch to, and benefit from, active post-progression therapies which do not form part of the standard treatment pathway, a standard ITT analysis may inaccurately estimate the ''true'' overall survival (OS) benefit associated with the investigational product. This will affect the cost-effectiveness analyses which make use of the OS evidence. Therefore, an adjustment of OS for non-standard 2nd line treatment in the ITT population was conducted. However, subsequent non-standard treatments received by patients at 3rd line or later were not able to be adjusted for. After correcting for bias due to switching at 2nd line treatment by using the inverse probability of censoring weighted (IPCW) method, enzalutamide was associated with a [redacted] reduction in the risk of death vs placebo [redacted]
- No head-to-head comparison of enzalutamide and abiraterone is available. An indirect treatment comparison (ITC) using the control arm of PREVAIL and of COU-AA-302 as the common arm was attempted to estimate the relative efficacy of enzalutamide versus abiraterone. However, the marked differences between these studies render the ITC inappropriate. The key difference relates to the different use of corticosteroids in the control arms of the studies (100% in COU-AA-302 vs 30.2% in PREVAIL). There is evidence to suggest that corticosteroids have a treatment effect on, at least, disease progression when given alone in the early stages of mHRPC. The impact of assuming parity between the control arms of PREVAIL and COU-AA-302 is the introduction of bias against abiraterone, in the estimation of relative treatment effect.
- Given the high potential for bias against abiraterone in the ITC, a naïve treatment comparison between enzalutamide and abiraterone has been chosen for the base case in the economic model[5,6]. However, as a result of differences in the patient population of PREVAIL and of COU-AA-302, in particular the inclusion in PREVAIL of patients with visceral disease, a naive comparison is likely to be biased against enzalutamide.
- To note, two weeks before the submission of this dossier to NICE, the outcomes of the final analysis of COU-AA-302 study were published in the Lancet Oncol[7]. The OS

results published by Ryan et al in Lancet Oncol differ slightly from the results presented at ESMO 2014[8] for the final analysis. Given the short time between publication in Lancet Oncol and this submission, Astellas could not implement the outcomes from Ryan et al in the ITC or economic model. Thus, in this document all reference to final results relate to those presented at ESMO 20148.

Cost-Effectiveness

- A cost-utility analysis (CUA) was performed using a Markov model based on three health states: stable disease, progressive disease and death. The model captures costs and quality of life associated with each health state as well as AEs and SREs. However, based on current clinical guidelines and clinical practice in the UK, patients are likely to receive other active treatments once their disease has progressed. Therefore, the progressed disease health state was divided in three treatment states to model the UK treatment pathway.
- Key inputs for OS and PFS are derived from the PREVAIL study for enzalutamide and BSC, and from the COU-AA-302 study for abiraterone.
- To correct, as far as possible, for bias from treatment switching, OS as measured in the PREVAIL ITT population was adjusted for 2nd line treatments which differed from the expected clinical practice in England and Wales. However, it was not possible to adjust for non-standard treatments received at third line or later. Furthermore, as a higher proportion of patients in the placebo arm of PREVAIL received non-standard therapies at third line or later, any bias is likely to be against enzalutamide.
- The COU-AA-302 data used (IA3) was the latest full published data available at the time of analysis. While an attempt was made to adjust for subsequent treatments in the manufacturer's submission the rationale and methodology were unclear, and had minimal effect on the hazard ratio. Therefore the most appropriate comparison was the published IA3 with the 30 June 2014 adjusted Prevail data.
- Time to treatment discontinuation (TTD) was used as the primary indicator of disease progression within the health economic model as suggested by expert opinion[9].
- In line with previous submissions, the model includes only grade 3 or higher AEs which are reported for ≥2% for any treatment group. For abiraterone, grade 3 or higher AEs were taken from Rathkopf et al which report only those grade 3 or 4 AEs of special interest. This could have underestimated the rate of AEs with abiraterone. In addition, this rate was calculated as the difference in the rates between the abiraterone and the placebo arm. However, given that all patients on abiraterone received corticosteroids, this may underestimate the true rate of AEs with abiraterone.
- As no information on SREs in patients treated with abiraterone in the chemo-naïve setting was available, it was conservatively assumed that abiraterone shows the same probability of experiencing a SRE as enzalutamide. However, given that all patients in the abiraterone arm received corticosteroids, this assumption is likely to underestimate the true incidence rate of SREs with abiraterone.
- The pairwise results of the base case analysis are presented in Table 1 and Table 2. Enzalutamide has an ICER of £27,076 per QALY gained versus abiraterone and £78,587per QALY gained versus BSC. These ICERs should be interpreted with caution as the agreed enzalutamide discount has not been included.

Table 1: Base-case pairwise cost-effectiveness results with list prices for enzalutamide and abiraterone

	Enzalutamide	Abiraterone	BSC
Technology acquisition cost*	£68,213	£63,203	£0
Other costs	£16,626	£17,469	£36,296
Total costs	£84,840	£80,672	£36,296
Difference in total costs	-	£4,168	£48,543
LYG	3.064	2.860	2.612
LYG difference		0.20	0.452
QALYs	2.274	2.120	1.657
QALY difference		0.154	0.618
ICER		£27,076	£78,587

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.
* Technology acquisition costs differ due to length of time on treatment rather than different prices.

Table 2: Incremental cost-effectiveness results with list prices for enzalutamide and abiraterone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (QALYs)	ICER incremental analysis (QALYs)
A: BSC	36,296	2.612	1.657	0	0	0	Not applicable	Not applicable
B: Abiraterone	80,672	2.860	2.120	44,375	0.248	0.464	£95,685	Extended dominance by ENZA
C: Enzalutamide	84,840	3.064	2.274	48,543	0.452	0.618	£78,587	£78,587 vs. BSC (£27,076 vs. ABI)

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; ICER incremental analysis: compares the treatment in the current row with the last non-dominated treatment option.

- Extensive scenario analyses and deterministic sensitivity analyses showed that the model results were robust. The probabilistic sensitivity analyses showed a 59% probability of enzalutamide being cost-effective versus abiraterone at a willingness to pay (WTP) of £30,000 per QALY gained. Although this will change when PAS discounts are applied.
- A scenario analysis to review the cost-effectiveness of enzalutamide taking into account the Pharmaceutical Price Regulation Scheme (PPRS) was included. Under this scheme, overspend on expenditure on branded medicines is repaid to the Department of Health by PPRS member companies. As the PPRS guarantees the NHS budget for medicines, it represents a key factor to be taken into account when assessing whether use of a particular treatment represents good use of NHS resources. The 2015 payment percentage of 10.36% was applied in a scenario analysis. This scenario resulted in an ICER of £23,642/QALY vs abiraterone compared to the base case ICER of £27,076/QALY. The ICER of this scenario was £69,911/QALY vs BSC, compared to the base case ICER of £78,587/QALY.

Budget Impact

- The NHS budget impact of the recommendation of enzalutamide in chemo-naive mHRPC will be somewhat negated by the current expenditure on abiraterone and

enzalutamide via the Cancer Drugs Fund in England. In the most recently available data from the CDF, between October 2013 and September 2014 there were 2,729 notifications for abiraterone in chemo-naive mHRPC; and 82 for enzalutamide in September 2014.

- Additionally it is highly likely that the current NHS expenditure on NICE approved post-chemo mHRPC drugs (enzalutamide and abiraterone) will reduce markedly once the drugs are routinely available for chemo-naive patients through the NHS.

Conclusion

- Enzalutamide is a highly effective and well tolerated drug for the treatment of men with mHRPC who are asymptomatic or mildly symptomatic and in whom chemotherapy is not yet clinically indicated. Enzalutamide has demonstrated a statistically significant benefit in OS, rPFS, PSA response rate and HRQL vs placebo. In addition, when compared with abiraterone, enzalutamide may offer financial and health resource utilisation benefits by requiring less routine product specific monitoring for liver toxicity, hypokalaemia, fluid overload and blood pressure, therefore avoiding associated hospital visits and clinician contact.
- Given the treatment benefit over BSC in the chemo-naïve setting as well as the flexibility to be prescribed without concomitant steroids, the option of being administered with or without food, and no additional need for patients to be monitored for hypokalaemia, fluid overload, high blood pressure or liver toxicity when compared with abiraterone, enzalutamide is expected to be a welcome therapeutic option to current standard of care for these patients in England and Wales.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name1: XTANDI™.

Approved name: Enzalutamide

Therapeutic class: The World Health Organisation International Working Group for Drug Statistics Methodology has assigned the following therapeutic class to enzalutamide[10].

- L: Antineoplastic and immunomodulating agents
- L02: Endocrine therapy
- L02B: Hormone antagonists and related agents
- L02BB: Anti-androgens
- L02BB04: Enzalutamide.

1.2 What is the principal mechanism of action of the technology?

Enzalutamide, formerly known as MDV3100, is a novel oral androgen receptor (AR) signalling inhibitor which has shown a significant treatment benefit in adults with different stages of metastatic hormone-relapsed prostate cancer (mHRPC).

At present, enzalutamide is indicated for:

- The treatment of adult men with mHRPC whose disease has progressed on or after docetaxel therapy1 (here-in referred to as "post-chemotherapy" setting).

- The treatment of adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated. This is the indication Astellas Pharma Ltd (Astellas) wish enzalutamide to be assessed in.

Evidence demonstrating the efficacy and safety of enzalutamide in the post-chemotherapy setting originates from AFFIRM[11], an international, randomised, double-blinded, phase III placebo-control study. In AFFIRM, enzalutamide showed a clinically meaningful and statistically significant prolongation of overall survival (OS) and radiographic progression-free survival (rPFS) versus placebo in this indication. AFFIRM was the study used for market authorisation in this indication.

Evidence demonstrating the efficacy and safety of enzalutamide in the chemo-naïve setting comes from the randomised, double-blind placebo-controlled phase III trial, PREVAIL[2]. PREVAIL was the study used for marketing authorisation in the chemo-naïve indication and forms the basis of this submission.

Prostate cancer which is not suitable for or has failed interventions of curative intent is usually initially androgen sensitive and can respond dramatically and beneficially to ADT, whether by surgical castration or inhibition of androgen production using luteinising hormone releasing hormone (LHRH) agonists or antagonists[12].

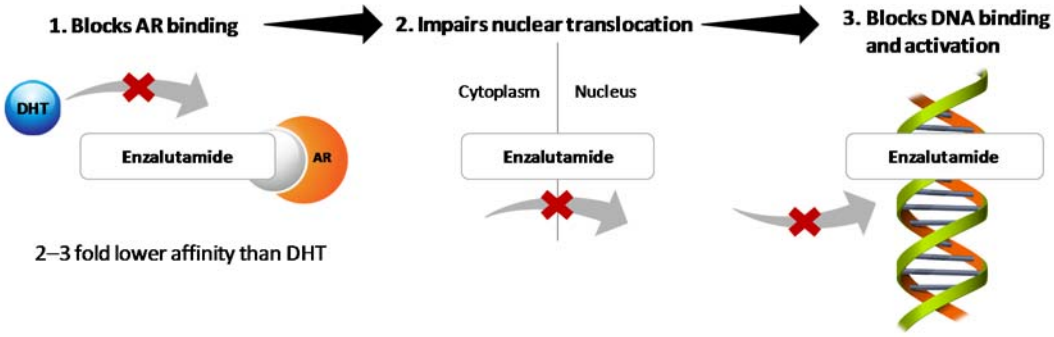
Over time, however, the majority of patients develop resistance to primary androgen ablation, and their disease becomes “hormone-relapsed”[13]. Increasing evidence has shown that despite low or even undetectable levels of androgen, AR signalling remains active and continues to drive disease in hormone-relapsed prostate cancer (HRPC)[14]. Stimulation of prostate cancer cell growth via the AR requires nuclear localisation and DNA binding[15].

Enzalutamide is an AR signalling inhibitor specifically selected for activity in models of mHRPC[16]. Unlike other AR inhibitors such as bicalutamide[17], enzalutamide blocks the AR signalling pathway at three different levels[11] (Figure A1):

1. Competitively inhibits binding of androgens to ARs in the interior of prostate cells (cytosol)
2. Inhibits the nuclear translocation of activated receptors
3. Inhibits the association of the activated AR with DNA even when AR is over-expressed and in prostate cancer cells resistant to anti-androgens.

Thus, enzalutamide acts as a pure AR antagonist in contrast to other AR inhibitors which in some situations can act as partial agonists[17].

Figure A1 Signalling steps inhibited by enzalutamide[16,18]



Abbreviation: AR: androgen receptor; DHT: dihydrotestosterone.

The ultimate consequence of the action of enzalutamide on AR signalling is:

- Reduced expression of AR-dependent genes
- Decreased growth of prostate cancer cells
- Induction of cancer cell death
- Tumour regression.

The mechanism of action of enzalutamide is different from abiraterone, a selective inhibitor of androgen biosynthesis currently used as standard of care in the chemo-naïve setting in the UK. Similar to enzalutamide, abiraterone is indicated for the treatment of men with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated as well as in the post-chemotherapy setting[4].

Abiraterone irreversibly blocks cytochrome P17 (an enzyme involved in the production of testosterone), thereby stopping androgen synthesis in the adrenal glands, prostate tissue and the prostatic tumor4. This mechanism of action is associated with side effects which require management via administration of concomitant steroids4.

At present, abiraterone is not recommended by NICE in the treatment of chemo-naïve patients[19] but it is available in England through the CDF[20].

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Marketing Authorisation for XTANDI™ for the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated was granted on 28 November 2014.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

A risk management plan (RMP) was developed for enzalutamide in the treatment of men with mHRPC whose disease has progressed while being on or after docetaxel therapy. This RMP is expected to be extended to include the treatment of chemotherapy-naïve mHRPC patients.

Based on this RMP, safety information on enzalutamide has been included in its summary of product characteristics. In addition, Astellas is undertaking active pharmacovigilance for the following safety concerns:

- Seizures
- Hypertension
- Falls
- Hallucination
- Neutrophil count decreased
- Non-pathologic fracture
- Interactions with strong inhibitors or inducers of CYP2C8
- Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19.

Finally, Astellas agreed to perform a safety study to further assess the risks with enzalutamide for patients who are at a higher risk of seizures.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The indication Astellas wish NICE to assess enzalutamide in is for the treatment of adult men with asymptomatic or mildly symptomatic mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are no ongoing studies involving enzalutamide that will provide additional comparative evidence in the next 12 months for the indication under review in this submission.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Enzalutamide is already launched in the UK for the treatment of adult men with mHRPC whose disease has progressed on or after docetaxel therapy1. Patients in England have been able to receive enzalutamide in the chemo naive indication since its inclusion on the CDF in October 2014.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Enzalutamide has regulatory approval throughout Europe, as well as in several other countries including the US, Canada and Australia for the treatment of mHRPC patients in the post-chemotherapy setting. In addition, in September 2014 the Food and Drug Association (FDA) approved XTANDI in the chemo-naïve setting[21].

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Enzalutamide is currently being appraised by the AWMSG and the SMC. Dossier submission dates were 14 January 2015 and 2 February 2015 respectively.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

Pharmaceutical formulation	**Enzalutamide**
Acquisition cost (excluding VAT)	Four cardboard wallets, each containing 28 soft capsules in PVC/PCTFE/aluminium blister (28 capsules per wallet; 4 wallets per carton). Price of 112 capsules: £2,734.67 [redacted]
Method of administration	A single oral daily dose.
Doses	160 mg (four x 40 mg capsules)
Dosing frequency	Daily until disease progression following clinical assessment. Time of dosing is independent of food administration.
Average length of a course of treatment	In PREVAIL, the randomised, double-blind, placebo-controlled study used for approval of enzalutamide in the chemotherapy-naïve setting, the median rPFS as assessed by the investigator was 19.7 months for patients receiving enzalutamide (95% CI: 18.1, 22.3)2. In this trial, the decision to discontinue treatment was based on a combination of criteria: confirmed radiographic disease progression or a SRE, and the initiation of cytotoxic chemotherapy or an investigational agent for treatment of prostate cancer. Therefore, time to treatment discontinuation (TTD) was also assessed as it is considered to reflect more accurately treatment duration in clinical practice than rPFS. Median TTD was 17.7 (95% CI [16.6; 19.4]) months for the enzalutamide arm. Duration on treatment in clinical practice may be less than that observed in PREVAIL.
Average cost of a course of treatment	Treatment cost: • Assuming mean exposure of 15.8 months as observed in PREVAIL: £46,969 [redacted] with a daily cost of £97.67 [redacted]
Anticipated average interval between courses of treatments	Enzalutamide is administered daily until disease progression. There is no clear evidence that continuing its administration beyond progression is associated with additional benefits. In clinical practice, patients progressing while being on enzalutamide will be likely switched to chemotherapy provided that they are fit to receive it. If patients are not eligible for chemotherapy, they will receive palliative care or it may be envisaged to give other treatments such as antiandrogen therapy (i.e., bicalutamide, nilutamide, flutamide), approved immunotherapy, oestrogen, and investigational agents for prostate cancer.
Anticipated number of repeat courses of treatments	There is no evidence to support immediate repeat treatment with enzalutamide after clinical disease progression.
Dose adjustments	If a patient experiences a Grade 3 or higher toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to Grade 2 or lower, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted1. No dose adjustments are necessary for1: • Patients with mild hepatic impairment. Caution is advised in patients with moderate hepatic impairment. Enzalutamide is not recommended in patients with severe hepatic impairment • Patients with renal impairment: No dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment or end-stage renal disease) • Elderly patients.

Pharmaceutical formulation	Enzalutamide
	The concomitant use of strong CYP2C8 inhibitors should be avoided1: • If a strong CYP2C8 inhibitor needs to be administered, the dose of enzalutamide should be reduced to 80 mg once daily • If co administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor

Abbreviations: rPFS: radiographic progression-free survival; PAS: patient access scheme.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No specific test is required to assess the eligibility of patients. Enzalutamide is an oral treatment self-administered by the patient. No special facilities are needed for enzalutamide administration1.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Enzalutamide does not require specified monitoring such as liver function tests (LFT) or cardiovascular monitoring which in turn reduces the need of visits to the nurse or clinic1. This can be considered a major advantage over abiraterone (currently available through the CDF for chemo-naïve patients[20]), for which liver function tests need to be performed every two weeks for the first three months of treatment, and monthly thereafter, as well as monthly monitoring of blood pressure, serum potassium and fluid retention4 all of which may be associated with an increase in the number of clinic visits and blood tests required. This may add to the burden of disease particularly if the patient needs to be taken by NHS transport services (estimated to be 10% of patients by clinical experts) or a relative, to have their blood investigations completed. Reduced LFT monitoring is also perceived to be an advantage by physicians who may not have a process in place to ensure timely interpretation of test results[22].

In circumstances where enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9, such as warfarin or acenocoumarol, additional international normalised ratio (INR) monitoring should be conducted1. Patients taking medicinal

products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19, or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate[1].

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Like all other treatments in this patient population, enzalutamide is likely to be administered with LHRH agonists in clinical practice.

Enzalutamide is well tolerated and unlike abiraterone, the only alternative pharmacological option available for chemotherapy-naïve mHRPC patients in the UK, enzalutamide does not need to be administered with concomitant corticosteroids, but can be at the discretion of the clinician[1].

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

HRPC is an advanced stage prostate cancer when the disease shows signs of progression despite castrate levels of testosterone. Patients with hormone-relapsed disease in whom cancer cells have metastasised from the prostate to other parts of the body, most notably the bones and lymph nodes are said to have mHRPC, and it is the presence of metastatic disease which is often associated with symptoms[12].

In the early stages, prostate cancer is localised to the prostate and driven by androgens[23]. At this stage, the disease may be treated with surgery or radiotherapy, or depending on the risk/benefit conservative management may be adopted (active surveillance)[12]. Patients who have inoperable locally advanced or metastatic disease at diagnosis or who have inoperable recurrent disease are treated with ADT as the disease is usually 'hormone sensitive' at this stage[12,24].

As the disease progresses, the tumour ceases to respond to androgen deprivation and becomes hormone-relapsed. HRPC tumours are not sensitive to ADT but may respond to therapy with anti-androgens (or anti-androgen withdrawal), inhibitors of androgen production, and estrogenic agents that further inhibit luteinising hormone (LH)[25]. However, the rate of response to these treatments is limited. In addition, in the case of oestrogens although they have been shown to suppress testosterone levels, they are associated with cardiotoxicity and related mortality and thus, prevention measures need to be taken[12,26].

At the point of diagnosis of HRPC, most patients (84%) will also have metastatic disease[27]. Of the patients with no metastases present at diagnosis of HRPC, 33% can expect to develop them within 2 years[27].

The prevailing mechanism underlying HRPC involves AR signalling being activated despite castrate levels of androgens[28,29]. The ongoing production of androgens by the adrenals and prostate cancer cells themselves are thought to be key mechanisms of ongoing AR signalling along with AR gene amplification and over expression[17].

Most patients receive two or more hormonal manipulations and are then offered chemotherapy as they continue to progress[30,31]. Chemotherapy (mainly docetaxel) is given to men with symptomatic progression. If patients are not yet symptomatic, patients receive BSC or abiraterone, the latter via the CDF[20]. In these patients, abiraterone has shown to significantly increase OS as well as rPFS vs BSC.

Because many of the hormone-relapsed tumours overexpress androgen receptors, second generation anti-androgens such as enzalutamide have been found to be effective in patients who have failed ADT.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Enzalutamide is currently indicated in the treatment of adult men with mHRPC whose disease has progressed on or after docetaxel therapy1. The number of patients eligible for enzalutamide in 2014 in England and Wales for this indication has been estimated as approximately 3,000[32].

In addition, the number of chemotherapy-naïve patients who would be eligible for enzalutamide in its indication extension is considered to be approximately 1,362 in 2015 and 5,616 in 2019. These estimates have been calculated using the following assumptions:

- Annual prevalence of mHRPC in England[33] and Wales[34] in estimated as 12,172 in 2015 and to 12,642 in 2020.
- Of men with mHRPC, 60% are estimated to be chemo-naïve[35]. Of these, 76% would be asymptomatic or mildly symptomatic, i.e., would have a BPI ≤3[36].
- In our estimates we assume that enzalutamide would become available at end of Q3 in 2015. Thus, only 25% of new cases in 2015 would be eligible for enzalutamide. It is presumed that the other patients would have already commenced on abiraterone.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

No life-expectancy data are available for chemotherapy-naïve patients with mHRPC in England and Wales. In the PREVAIL trial, a randomised, double-blind placebo-controlled study comparing the efficacy and safety of enzalutamide and placebo in the treatment of patients with asymptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet clinically indicated median OS in the most mature cut-off analysis conducted to-date (775 events) was 33.51 months and 30.98 months for enzalutamide- and placebo-treated patients, respectively[37]. To note, this data cut-off has been conducted for modelling purposes.

In PREVAIL, a proportion of patients were enrolled in the UK (N=153/1,717; 8.9%). No specific analysis has been conducted for UK patients only. The OS in real clinical practice is expected to be similar to that observed in the PREVAIL and COU-AA-302

trials. Both trials included European patients and the baseline characteristics of these patients reflect those of patients in clinical practice in the UK.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Currently approved therapies for asymptomatic or mildly symptomatic chemotherapy-naïve mHRPC patients include abiraterone4 and sipuleucel-T[38]. Both are still under review by NICE[19]. The sipuleucel T guidance is expected to be published in February 2015[39]. It is unclear when the abiraterone guidance will be published, but abiraterone is already available in England through the CDF.

In January 2014, NICE updated the previous prostate cancer guidelines on diagnosis and treatment (NICE Clinical Guideline [CG] 58). The updated guideline is the NICE CG 175[31]. This clinical guideline covers treatment throughout the whole spectrum of prostate cancer management; from diagnosis and screening through to palliative care, including management of mHRPC. The recommendations for mHRPC in NICE CG 175 are based on the NICE technology appraisal guidance 101 (i.e., docetaxel for the treatment of hormone-refractory prostate cancer). NICE CG 175 does not provide any recommendations specifically for asymptomatic or mildly symptomatic mHRPC patients for whom chemotherapy is not yet clinically indicated[31].

The guideline recommends docetaxel, within its licensed indications, as a treatment option for men with mHRPC only if their Karnofsky performance-status is ≥60%. This guideline also recommends offering dexamethasone (0.5 mg daily) in patients after ADT and anti-androgen therapy. NICE CG 175 does not incorporate any statements regarding the possible use of abiraterone, enzalutamide or sipuleucel-T when patients fail to respond to ADT and for whom immediate chemotherapy is not yet clinically indicated.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

As already explained in the previous section, the latest NICE guideline CG175 does not provide any specific recommendations regarding treatment of mHRPC patients in whom immediate chemotherapy is not yet clinically indicated. This guideline does not yet capture the outcome of the NICE TA259 (i.e., “abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen”) or TA316 (i.e., “enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen”).

NICE is currently assessing radium-223 dichloride. Final recommendation has not yet been issued but after a second appraisal consultation NICE have provided preliminary recommendation for radium-223 in the treatment of adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases, only if[40]:

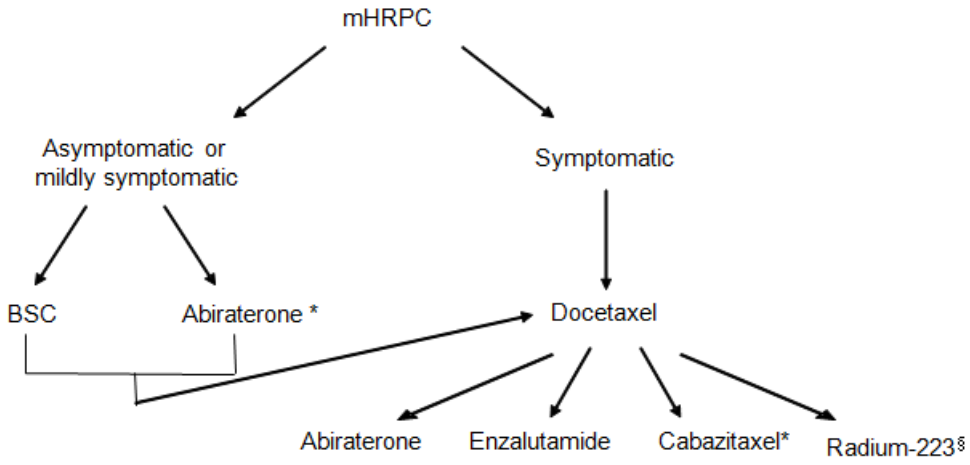
- They have had treatment with docetaxel and
- The company provides radium-223 dichloride with the discount agreed in the patient access scheme.

The latest European Urology Association (EAU) guidelines[12] (published in 2014) recommend initiating chemotherapy with docetaxel every three weeks if the mHRPC patient who has failed to ADT is symptomatic but do not provide any clear guidance for those patients who are not yet symptomatic. For these patients no clear-cut recommendation can be made regarding the most effective drug for secondary treatment (i.e. hormonotherapy or chemotherapy) as no clear predictive factors exist.

The treatment pathway presented in Figure A2 has been constructed based on the latest EAU guidelines and several NICE guidance documents.

The outcomes in the PREVAIL trial (both co-primary endpoints as well as all secondary and exploratory endpoints were met at the different data cut-offs) together with the fact that no product-related monitoring is needed with enzalutamide suggests that it will be the treatment of choice (over abiraterone) in asymptomatic or mildly symptomatic mHRPC patients in whom immediate chemotherapy is not yet clinically indicated.

Figure A2 Current treatment algorithm of mHRPC in England clinical practice



Source: Mottet et al[12]; NICE recommendation for abiraterone in the chemotherapy-naïve setting[19]; TA101 docetaxel[41]; TA225 cabazitaxel[42]; TA259 abiraterone[43]; TA316 enzalutamide[44].
*Following a negative NICE recommendation, cabazitaxel in the post-chemotherapy setting are available through the CDF on a case by case basis, in England, although this is due to change from March 2015.
Abiraterone is widely used in England via the CDF; the NICE appraisal is ongoing
§NICE has given preliminary recommendations for radium 223 to be given to symptomatic patients in the post-chemotherapy setting[40].

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Prior to the licence of abiraterone in the chemo-naïve setting, physicians had a very limited choice of therapies for patients with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT and in whom immediate chemotherapy is not yet clinically indicated. The options were limited to best supportive care (BSC) and symptomatic treatment until chemotherapy becomes indicated. Symptomatic treatment comprises: radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies and corticosteroids.

Abiraterone has shown a significant increase in rPFS compared with BSC[82,83]. In addition, despite not reaching statistical significance in OS in the first three interim analysis, it showed a significantly greater OS in the final analysis8. However, its clinical outcomes may be associated with several clinical considerations.

Firstly, abiraterone has been associated with serious hepatotoxicity requiring regular monitoring of the liver function4. Liver function test elevations (ALT or AST increases of > 5 times upper limit normality (ULN)) or bilirubin increases >1.5 times ULN were reported in approximately 4% of patients who received abiraterone acetate in the abiraterone clinical studies, typically during the first 3 months after starting treatment4. Enzalutamide is not associated with hepatotoxicity and therefore it does not need regular monitoring of liver function1. As such, less monitoring and associated hospital visits are anticipated for patients treated with enzalutamide. Additionally, given its mechanism of action, abiraterone leads to a mineralocorticoid excess and thus, patients also require fluid retention, hypertension and hypokalaemia to be monitored.

Secondly, abiraterone must be taken without food, to avoid increasing systemic exposure4. This may have a significant impact on the lifestyle of the patient. Enzalutamide can be taken with or without food allowing patients flexibility and simplifying self-medication1.

Lastly, abiraterone must be administered with steroids to reduce the effects of mineralocorticoid excess inherent from its mechanism of action4 with the consequent complications of long term steroid use. Enzalutamide can be administered with or without steroids, allowing patients and clinicians the option of avoiding the steroid related side-effects if clinically appropriate1.

Exposure to enzalutamide or abiraterone in the chemo-naïve setting may lead to changes in the post-chemo treatment algorithm in the UK. Currently, when patients become symptomatic they receive docetaxel[31]. Patients remain on this agent until disease progression if they tolerate this therapy[31]. Upon disease progression after or during treatment with docetaxel, patients move to (post-chemo) enzalutamide or abiraterone[31]. However, lack of evidence on the efficacy of post-chemo enzalutamide and abiraterone in patients previously exposed to these agents in the chemo-naïve setting brings uncertainty as to whether chemo-naïve enzalutamide and abiraterone will replace their use in the post-chemo setting.

Although not recommended by NICE, patients can also receive post-chemo cabazitaxel through the CDF. However, cabazitaxel is expected to be delisted from the CDF in March 2015[45]. Consequently, it may no longer be available to post-chemo patients in the UK.

2.7 Please identify the main comparator(s) and justify their selection.

The comparators considered in the health economic model are in line with NICE final scope for this indication: abiraterone and BSC. At present there are two treatments approved in Europe for the treatment of mHRPC the chemo-naïve setting: abiraterone and sipuleucel-T. Of these, only abiraterone (Zytiga, Janssen-Cilag Ltd) is available in England in the chemotherapy-naïve setting. Although it is not currently recommended by NICE[19] it is widely used in England through the CDF[20]. There is no access to chemo naïve abiraterone in Wales.

It is estimated that around 53%[*] of all patients within this licensed indication are already receiving abiraterone via the Cancer Drugs Fund. Abiraterone can be considered the standard of care for this indication.

BSC includes: LHRH analogues (if not surgically castrated), corticosteroids, blood transfusion, bisphospohonates, radiotherapy, analgesics and palliative surgery to treat skeletal-related events (SREs), when needed.

The evidence of the clinical efficacy of enzalutamide in the reviewed indication comes from a randomised, double-blind placebo-controlled phase III study known as PREVAIL. The comparator arm in this study was placebo plus BSC. No head-to-head study comparing enzalutamide to abiraterone has been conducted in the chemotherapy-naïve setting. Therefore, a systematic literature review was performed to identify the evidence that would allow an indirect treatment comparison (ITC) between these two therapies.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In PREVAIL, the overall incidence of adverse events (AEs) with enzalutamide was comparable to that with placebo2. The safety profile of enzalutamide 160 mg daily is considered acceptable and generally manageable with basic pharmacological treatment when needed. AEs were generally mild and resulted in infrequent dose reductions, dose interruptions, or discontinuations2. The most common all grade adverse drug reactions were fatigue and nausea2.

[*] The eligible number of patients is 5,446 for England and Wales (see Table C1). England population is 94.28% of England and Wales population [Source: Office for National Statistics] therefore the eligible patient population in England is 5,134. In the CDF there were 2,729 notifications for chemo-naïve abiraterone between October 2013 and September 2014. Therefore it is estimated that 53% of the eligible population are already receiving abiraterone.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As enzalutamide is administered orally at the patient's home there are no anticipated costs due to location of care, staff or administration. Unlike abiraterone2, regular monitoring for liver toxicity, hypokalaemia and fluid retention is not needed for patients on enzalutamide1. This may lead to resources saving. Not needing to be administered with steroids may also lead to resource savings as these patients will not be exposed to the toxicity associated with long-term use of steroids.

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is anticipated. In contrast to abiraterone2, enzalutamide does not require any product-specific monitoring1, and may lead to fewer physician and/or hospital contacts.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Astellas are not aware of any issues relating to equality or equalities in NICE guidance or protocols of the treatment of patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Enzalutamide is anticipated to be the treatment of choice in patients with asymptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet clinically indicated.

Enzalutamide is the first and only AR antagonist that blocks the AR signalling pathway at three distinct levels:

1. Competitively inhibits binding of androgens to AR in the cytosol
2. Inhibits the nuclear translocation of activated receptors
3. Inhibits the association of the activated androgen receptor with DNA.

In the PREVAIL study, the mechanism of action of enzalutamide was translated into a significant longer OS and PFS than BSC with comparable safety profile and tolerability2.

Enzalutamide also offers a mechanism of action that is distinct to that of abiraterone acetate, an androgen biosynthesis inhibitor that inhibits the enzyme cytochrome P450 17 (CYP17)4. Abiraterone thus inhibits synthesis of androgens but does not have any subsequent effect on the AR signalling pathway.

The main advantages of enzalutamide over abiraterone can be summarised as follows:

- Unlike abiraterone, enzalutamide can be administered without steroids. Steroids are not clinically indicated for treatment with enzalutamide and therefore their side effects (especially those associated with long term use) can be avoided.
- Enzalutamide does not require regular liver, electrolyte, or fluid balance monitoring compared to abiraterone.
- Enzalutamide can be administered with or without food in contrast to abiraterone where absorption is modified by food intake. Experts have reported that this is a significant benefit and is a frequently reported source of concern/enquiry for patients currently taking abiraterone, in particular for those patients who have concomitant medications to consider.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

All health benefits will be included in the QALY calculation.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	As per the final scope	Not applicable
Intervention	Enzalutamide	Enzalutamide once daily 160 mg (four x 40 mg) capsules	Not applicable
Comparator(s)	• Abiraterone in combination with prednisone or prednisolone • BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids).	As per the final scope	As per the final scope
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (radiographic and prostate specific antigen response) • Time to initiation of chemotherapy • Response rate • Adverse effects of treatment • Health-related quality of life (HRQL).	In addition to the outcomes listed in the final scope, the manufacturer wish to present data on time to treatment discontinuation (TTD)	TTD is considered a more accurate reflection of what happens to mHRPC patients in clinical practice than rPFS. This end point has previously been accepted by NICE.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access scheme for the intervention or comparator technologies should be taken into account.	As per the final scope	
Subgroups to be considered	None	None	
Special considerations, including issues related to equity or equality	None	None	

Section B – Clinical and cost-effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review (SLR)[46] was conducted to identify clinical evidence regarding the efficacy and safety of enzalutamide and comparator drugs as outlined in the scope, and to inform an indirect treatment comparison (ITC). The SLR has been conducted as part of due diligence to prepare for European submissions including the NICE submission. Thus, the SLR undertaken by Astellas aimed at identifying all relevant efficacy and safety evidence for enzalutamide and all other treatment agents currently authorised in Europe for chemotherapy-naïve mHRPC patients. However, only the outcomes relevant to the decision problem are presented in this submission.

The search strings used for the SLR were not specific for enzalutamide and abiraterone but also encompassed the following interventions: docetaxel, radium-223 dichloride, and sipuleucel-T. The scope of the SLR included both randomised and non-randomised trials. The results for the studies with the comparator drugs are presented in section 6.7.

The databases searched for the SLR are detailed in Table B1. They were supplemented by manual searching of the bibliographies of relevant articles and with unpublished data from the manufacturer. Using Boolean operators, the searches combined terms (including MeSH headings as appropriate) for mHRPC, pharmacological intervention(s) of interest, and clinical trial design. The search strategy is provided in section 10.2.

Table B1 Databases searched for clinical review

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process (via Ovid)	OvidSP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed

Database / information source	Interface / URL
EMBASE	OvidSP
Science Citation Index Expanded (SCI - Expanded) and Conference Proceedings Citation Index-Science (CPCI-S)	Web of Science
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library/Wiley Interscience
Health Technology Assessment Database (HTA)	Cochrane Library/Wiley Interscience
ClinicalTrials.gov	http://www.clinicaltrials.gov
International Clinical Trials Registry Platform (ICTRP)	http://apps.who.int/trialsearch/
metaRegister of Controlled Trials (mRCT)	http://www.controlled-trials.com/mrct/
NHS Economic Evaluation Database (NHS EED)	Cochrane Library/Wiley Interscience
Health Economic Evaluation Database (HEED)	EBSCOHost
EconLit	OvidSP
Cost-effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4
National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/index.html
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/en
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/index.html
U.S. Food and Drug Administration (FDA)	http://www.fda.gov/
European Medicines Agency (EMA)	http://www.ema.europa.eu/ema/
American Society of Clinical Oncology (ASCO) Annual Meeting and GU (ASCO-GU) Cancers Symposium	See SLR Report[46]
American Urological Association (AUA) Annual Meeting	See SLR Report[46]
European Association of Urology (EAU) Annual Congress	See SLR Report[46]
European Society for Medical Oncology (ESMO) Congress	See SLR Report[46]
European CanCer Organisation (ECCO) Congress	See SLR Report[46]
International Society for Quality of Life Research (ISOQOL) Annual Conference	See SLR Report[46]
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	See SLR Report[46]

Source: SLR Report[46]

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should

be provided to ensure that the rationale is transparent. A suggested format is provided below.

The inclusion and exclusion criteria applied in the selection of studies are listed in Table B2.

Table B2 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: • Studies in adults (over the age of 18) with asymptomatic, or mildly symptomatic, mHRPC AND who have not received prior chemotherapy, were eligible for inclusion in the review[†] Interventions: • The interventions were enzalutamide, abiraterone, docetaxel, radium-223 dichloride and sipuleucel-T. However, only studies including enzalutamide or abiraterone as an intervention or comparator are described here Outcomes: • The outcomes included in the systematic literature review included OS, PFS, rPFS, response rate, PSA response, time to chemotherapy initiation, time to antineoplastic therapy (cytotoxic or hormonal), time to SRE, time to PSA progression, best overall response, adverse effects of treatment, HRQL including time to pain progression, time to increase in analgesia and time to decline in performance status. • Of the outcomes listed above, only OS, rPFS, time to chemotherapy initiation, time to SRE, time to PSA progression and overall best response were to be included in the ITC. Study design: • Phase II and III, RCTs of any size and duration were eligible for inclusion in the clinical effects and safety review • Crossover RCTs were eligible if data were presented at crossover • Non-randomised comparative and uncontrolled studies were eligible for inclusion if they reported relevant clinical effectiveness or safety data for enzalutamide • Studies published as abstracts or conference presentations, as well as data from unpublished RCTs, were eligible for inclusion in the review if adequate data were provided. Systematic reviews were eligible for inclusion as a source of references to primary studies Language restrictions • Studies reported in languages other than English were

[††] Studies assessing mixed populations (i.e. where some patients had received chemotherapy and some had not) were included in the indirect treatment comparison for comparators where studies of chemotherapy naïve populations did not exist. However, the only study included for the indirect comparison vs abiraterone had enrolled chemo-naïve patients only.

	Clinical effectiveness
	identified and listed for information only
Exclusion criteria	Population: • Studies reporting on patients described as 'hormone sensitive' or 'castration sensitive' were not eligible for inclusion. Similarly, studies reporting on patients who had received prior chemotherapy were excluded Interventions • Studies that did not include any of the interventions listed in the inclusion criteria Outcomes • Studies that did not include any of the outcomes listed in the inclusion criteria Study design • Single arm studies except if they provided relevant clinical effectiveness or safety data for enzalutamide Language restrictions • No study reported in any language other than English was reviewed or included in the indirect treatment comparison

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (http://www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

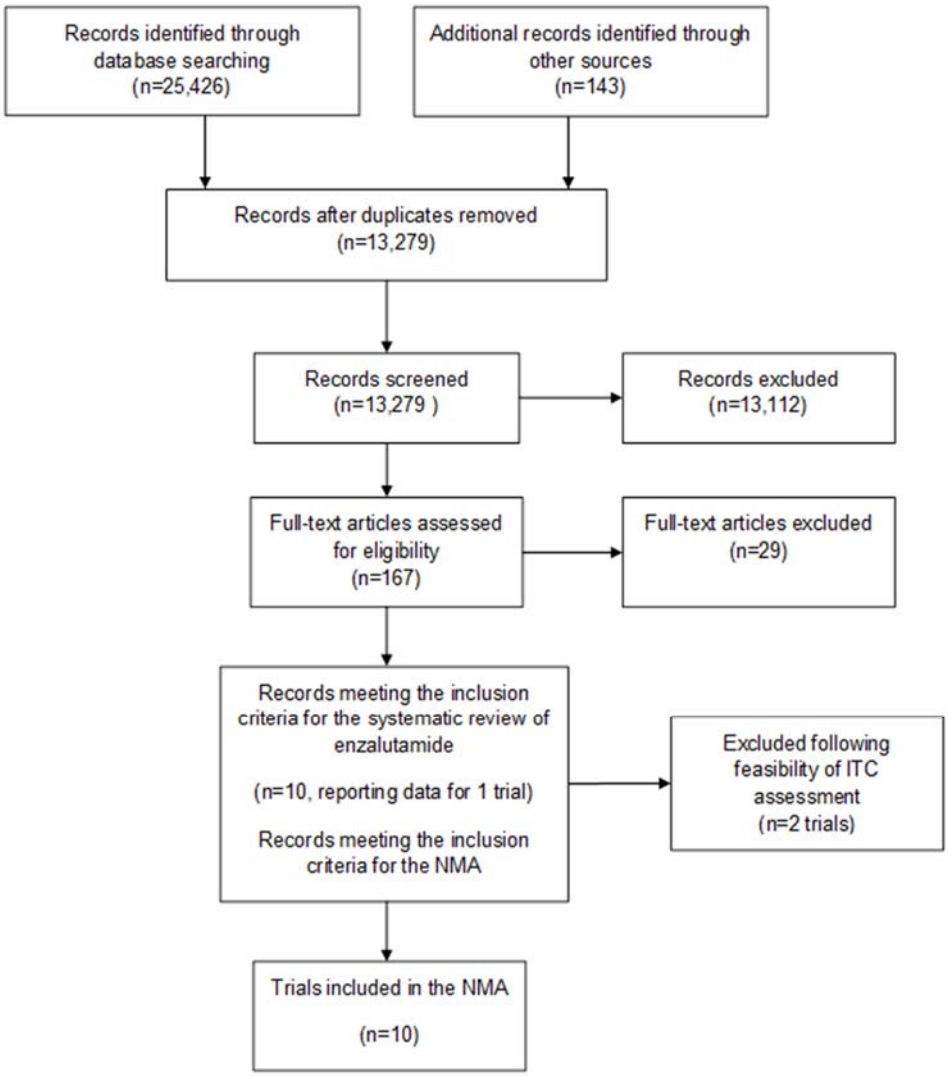
The searches for the SLR were conducted on 20 October 2014. The period covered by each search is detailed in Appendix 2, section 10.2.3.

Citations were first screened based on the title and abstract supplied with each citation. Those that did not match the eligibility criteria were excluded. Full-text copies of all references that could potentially meet the eligibility criteria were included at this stage.

The flow diagram below shows the records identified in each database as well as the number of records included and excluded from the SLR (Figure B1). The flow diagram includes all the studies identified in the SLR. As mentioned in section 6.1.1, the SLR aimed at identifying not only studies conducted with enzalutamide or abiraterone but also encompassed the following interventions: docetaxel, radium-223 dichloride, and sipuleucel-T.

The eligibility criteria were then applied to the full-text citations. At each stage two independent reviewers screened the abstracts/full text articles; any discrepancies were reconciled between both reviewers.

Figure B1 PRISMA flow diagram with the efficacy and safety studies of enzalutamide identified through the predefined search strategy



Of the 10 studies reported in the Prisma flow for the network meta-analysis, only two were included in the ITC comparing enzalutamide and abiraterone.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

PREVAIL is the only study that compares enzalutamide to any other treatment for adults with asymptomatic or mildly symptomatic mHRPC in whom immediate

chemotherapy is not yet clinically indicated (here-in referred to as the chemo-naïve setting). PREVAIL is a head-to-head study comparing enzalutamide 160 mg once daily to placebo. Management of patients in the placebo arm is considered the equivalent to BSC[12,31].

PREVAIL data presented in this submission are drawn from both published and unpublished sources:

- Published articles: Beer et al published in New England Journal of Medicine (NEJM)[3], Beer et al presented at ASCO 2014[47] and at ESMO 2014[48], Armstrong et al presented at ASCO 2014[49], Tombal at EAU 2014[50], Loriot et al at ESMO 2014[51] and Higano et al also at ESMO 2014[52]

- Unpublished: PREVAIL clinical study report (CSR)2, the patient reported outcome (PRO) report[53] and the OS adjustment report[37].

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

One study has been conducted with enzalutamide in adults with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated. This study is a phase III double-blind, placebo-controlled international study comparing enzalutamide versus placebo. The design of this study is summarised in Table B3.

Table B3 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
NCT01212991 (PREVAIL)	ENZA (N=872): • ENZA 160 mg PO OD Use of glucocorticoids was allowed but not required	PLA (N=845) • PLA PO OD Use of glucocorticoids was allowed but not required	• Patients with asymptomatic or mildly symptomatic mHRPC and in whom immediate chemotherapy is not yet clinically indicated • ECOG 0-1 • Visceral (lung and liver) disease was permitted	Beer et al3[,47,48] Armstrong et al[49] PREVAIL CSR2 PREVAIL PRO analysis[53]

Abbreviations: CSR: clinical study report; ENZA: enzalutamide; ECOG: eastern cooperative oncology group; OD: once daily; PLA: placebo; PO: per os (oral); PRO: patient reported outcomes.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

No head-to-head randomised controlled trial (RCT) comparing enzalutamide with abiraterone has been conducted as confirmed in the SLR, but an indirect comparison of the two therapies was attempted.

As stated in the scope, in England and Wales current treatment for patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated relies on BSC and abiraterone. In this respect, the latter is currently not approved by NICE[19] but patients in England have access to it through the CDF[20]. As such, abiraterone has rapidly assumed position as 'standard of care' in this group of patients. Therefore, the most appropriate comparator is now abiraterone, although in this review BSC is also considered a comparator.

In the PREVAIL trial, the placebo arm is considered to be equivalent to BSC, the only treatment available for the patient population of interest, when the trial was designed.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies were excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

The relevant non-RCTs identified during the SLR are provided in Table B4.

Table B4 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Scher et al	Enzalutamide (7 dose escalation cohorts receiving one of the following doses: 30, 60, 150, 240, 360, 480, and 600 mg per day)	Mixed population: • Chemo-naïve: N=12 • Post-chemo: N=12	The primary objective was to assess pharmacokinetics, safety, and tolerability, and to define a maximum tolerated dose	Scher et al[54]	It provides safety data on enzalutamide

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Primary data for this submission are derived from the pre-planned interim and final analyses for OS and rPFS, respectively, but also include data from more mature cut-offs for OS and rPFS (Table B5). The protocol pre-planned analyses have been published in Beer et al in the NEJM3. Data related to the January 2014 cut-off for OS have been published in NEJM3, but the data from the OS analysis used in the model (30 June 2014) have not yet been published (see section “List of definitions”).

Table B5 Data cut-off analyses conducted for PREVAIL

	Data cut-offs conducted	
	Pre-planned in the protocol	**Subsequent cut -offs**
OS	~516 events: 16 Sept 2013 (540 events)	15 January 2014 (656 events)* 30 June 2014 (775 events)
rPFS	~410 centrally confirmed events: 06 May 2012 (439 events)	16 Sept 2013 (889 events; Investigator assessed)

Abbreviations: OS: overall survival; rPFS: radiographic progression-free survival.
*The January 2014 data cut-off was carried out for safety update as part of the 90-day safety update submission to the FDA. An analysis of the OS endpoint was also conducted for the data with this cut-off date. The results of this analysis were published in the Appendix of Beer et al3. For simplicity, the results of this data cut-off are not included in this submission.

The methodology of this study, along with results of all data cut-off analyses except for the 30 June 2014 one, is available in the public domain (as reported in Beer et al3 and supplemented by abstracts presented at the ASCO[47,49] and ESMO[48] 2014 conferences). Additional details relating to the methodology of the study have been added to this document from the unpublished final CSR2, PRO report[53] and OS adjustment report[37].

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The methodology used in PREVAIL is summarised in Table B6.

Table B6 Summary of methodology of PREVAIL

Trial no. (acronym)	**PREVAIL**
Location	The study was conducted at 207 sites in 22 countries in North America, Europe, Australia, and Asia. Overall, 153 patients from the UK participated in this trial.
Design	PREVAIL was an international, randomised, double-blind, placebo-controlled, global multicentre phase III study comparing oral enzalutamide with placebo for efficacy and safety in adults with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated.
Duration of study	First and last randomisations took place in 28 September 2010 and 07 September 2012, respectively. The database was frozen in December 2013 but patients are still followed-up for survival data.

Trial no. (acronym)	PREVAIL
Method of randomisation	The study was centrally randomised by IVRS using a permuted block method. Randomisation was stratified by study site. Patients were randomised in a 1:1 ratio to receive oral enzalutamide (160 mg orally once daily as four 40-mg capsules) or matched placebo capsules.
Method of blinding (care provider, patient and outcome assessor)	All patients, investigators, site personnel and the sponsor's staff involved in the conduct of the study were blinded to treatment assignment. The Sponsor, sites, and patients remained blinded to study drug until the database had been locked on December 2013. An independent Data Monitoring Committee monitored and reviewed safety data on an ongoing basis.
Intervention(s) (n =) and comparator(s) (n =)	Intention-to-treat (ITT): N=1,717: • ENZA: N=872. • PLA: N=845.
Primary outcomes (including scoring methods and timings of assessments)	The co-primary efficacy endpoints of this study were OS and rPFS. OS was defined as the time from randomisation to death from any cause in the ITT population defined as all randomised patients. Survival time of living patients was censored at the last date a patient was known to be alive or lost to follow up. The OS distribution curve, median OS, and 95% CIs were estimated using the Kaplan–Meier method. OS data were assessed at the pre-planned interim analysis (scheduled at approximately 516 deaths) and at subsequent data cut-offs (Table B5). Radiographic progression-free survival (rPFS) was defined as time from randomisation date to the first objective evidence of radiographic disease progression assessed by independent central radiology review or death due to any cause within 168 days after treatment discontinuation, whichever was first. The rPFS distribution, median rPFS, and the 95% CIs were estimated using the Kaplan–Meier method. The different data cut-off dates are provided in Table B5. Regarding rPFS, data based on the investigator's assessment have also been analysed and are presented here-in. The protocol specified that the analysis of centrally-assessed rPFS was to be conducted at 410 events; the final analysis was conducted at 439 events. Given that the analysis of the investigator assessed rPFS includes a higher number of events (N=889), this is the analysis used in the economic model.
Secondary outcomes (including scoring methods and timings of assessments)	The secondary endpoints assessed in PREVAIL were: • Time to first documented skeletal related event (SRE) defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain • Time to initiation of cytotoxic chemotherapy defined as the time from randomisation to the date of initiation of cytotoxic chemotherapy • Time to prostate specific antigen (PSA) progression

Trial no. (acronym)	PREVAIL
	where PSA progression was defined according to the consensus guidelines of the PCWG2[55,56] • PSA response defined as a ≥50% reduction in PSA from baseline to the lowest postbaseline PSA value which required confirmation by a consecutive assessment at least 3 weeks later • Best overall soft tissue response on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
Exploratory outcomes	The study also included the following exploratory endpoints which were pre-specified in the study protocol: • Quality of life maintenance as assessed by functional assessment of cancer therapy – prostate (FACT-P) and EQ-5D • Brief Pain Inventory Short Form (BPI-SF) questionnaire • Time to first post-baseline antineoplastic therapy (cytotoxic, hormonal or investigational) • PSA response defined as a 90% or more decrease from baseline.
Duration of follow-up	Patients were to remain on the study drug until confirmed radiographic disease progression or a SRE, and either the initiation of cytotoxic chemotherapy or an investigational agent for treatment of prostate cancer. After permanent discontinuation of study drug, patients continued to be monitored in long-term follow-up for radiographic disease progression (unless disease progression was already confirmed), SREs (unless a SRE was previously documented), additional antineoplastic treatments for prostate cancer, and survival.

Source: PREVAIL Clinical Study Report2, Beer et al3, PREVAIL PRO report[53].
Abbreviations: BPI: brief pain inventory; CI: confidence interval; ENZA: enzalutamide; FACT-P: functional assessment of cancer therapy-prostate; ITT: intent-to-treat; IVRS: interactive voice and web response services; PCWG2: Prostate Cancer Clinical Trials Working Group; PLA: placebo; PSA: prostate specific antigen; RECIST: response evaluation criteria in solid tumours; rPFS: radiographic progression-free survival; SRE: skeletal-related events.

During the treatment phase, subjects had a safety assessment at the Day1/Week 1 Visit, the Week 2 Visit, every 4 weeks starting from the Week 5 Visit through the Week 25 Visit, and every 12 weeks thereafter. Efficacy assessments were performed at Weeks 13 and 25, and every 12 weeks thereafter2.

Patients received the first dose of enzalutamide (160 mg) or placebo on day 1 and continued daily dosing as long as study drug was tolerated and androgen deprivation therapy (ADT) continued. Treatment continued until confirmed radiographic disease progression or a SRE, and the initiation of cytotoxic chemotherapy or an investigational agent for treatment of prostate cancer. PSA rise without evidence of confirmed radiographic progression or a SRE was strongly discouraged as a criterion to start a new systemic antineoplastic therapy during the first 12 weeks of therapy or throughout the study as per Prostate Cancer Clinical Trials Working Group 2

(PCWG2) guidelines. After randomisation, radiation therapy and initiation of bisphosphonates or other approved bone-targeting agents were allowed2.

Patients were evaluated every 4 weeks through week 49 and then every 12 weeks thereafter. Patients had a safety follow-up visit 28 days after the last dose of study drug or before initiation of cytotoxic chemotherapy or an investigational agent, whichever was first. Following the treatment period, all patients were monitored in long-term follow-up for survival status, subsequent treatments for prostate cancer, SRE (if a SRE was not documented previously), and radiographic progression (if radiographic progression was not confirmed previously). The visit schedule for patients during long-term follow-up was identical to the visit schedule for patients remaining on treatment (every 4 weeks through week 49 and every 12 weeks thereafter)2.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Study selection criteria are listed in Table B7. Briefly, patients were eligible for enrolment if they had histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per decilitre [1.7 nmol per litre]), progressive disease despite being on ADT, had not been previously exposed to chemotherapy, were asymptomatic or mildly symptomatic and immediate chemotherapy was not yet clinically indicated.

Table B7 Eligibility criteria in PREVAIL

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
PREVAIL	• Age 18 or older and willing and able to provide informed consent • Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features • Ongoing ADT defined as a GnRH analogue or bilateral orchiectomy • Patients who had not had a bilateral orchiectomy, had to have a plan to maintain effective GnRH analogue therapy for the duration of the trial • Serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit • Patients on bisphosphonate	• Severe, concurrent disease, infection, or comorbidity that, in the judgement of the investigator, would make the patient inappropriate for enrolment • Known or suspected brain metastasis or active leptomeningeal disease • History of another malignancy within the previous 5 years other than curatively treated nonmelanoma skin cancer • Absolute neutrophil count < 1500/μL, or platelet count < 100,000/μL, or haemoglobin < 5.6 mmol/L (9 g/dL) at the screening visit • Total bilirubin, ALT or AST > 2.5-times the upper limit of normal at the screening visit • Creatinine > 177 μmol/L (2 mg/dL) at the screening visit • Albumin < 30 g/L (3.0 g/dL) at the screening visit

	therapy had to have been on stable doses for ≥4 weeks • Progressive disease at study entry defined as ≥1 of the following criteria while being on ADT: - PSA progression defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. Patients who received an antiandrogen had to have had progression after withdrawal. The PSA value at the screening visit had to be ≥2 µg/L (2 ng/mL) - Soft tissue disease progression defined by RECIST 1.1 - Bone disease progression defined by PCWG2 with 2 or more new lesions on bone scan • Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible • No prior cytotoxic chemotherapy for prostate cancer • Asymptomatic or mildly symptomatic from prostate cancer (i.e., < 4 on BPI question 3) • ECOG performance status 0–1 • Estimated life expectancy ≥6 months • Able to swallow the study drug and comply with study requirements	• History of seizure or any condition that may predispose to seizure. Also, history of loss of consciousness or transient ischemic attack within 12 months of enrolment (day 1 visit) • Clinically significant cardiovascular disease including myocardial infarction within 6 months; uncontrolled angina within 3 months; congestive heart failure New York Heart Association class III or IV, or patients with history of congestive heart failure New York Heart Association class III or IV in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months results in a left ventricular ejection fraction that is ≥ 45%; history of clinically significant ventricular arrhythmias; history of Mobitz II second degree or third degree heart block without a permanent pacemaker in place; hypotension as indicated by systolic blood pressure < 86 mm Hg at the screening visit; bradycardia as indicated by a heart rate of < 50 beats per minute on the screening ECG; uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at the screening visit • Gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease within last 3 months) • Major surgery within 4 weeks of enrolment (day 1 visit) • Use of opiate analgesics for pain from prostate cancer within 4 weeks of enrolment (day 1 visit) • Radiation therapy for treatment of the primary tumour within 3 weeks of enrolment (day 1 visit) • Radiation or radionuclide therapy for treatment of metastasis • Treatment with flutamide, 5-α reductase inhibitors, estrogens, cyproterone, systemic biologic therapy for prostate cancer (other than approved bone targeted agents and GnRH analogue therapy) or other agents with antitumor activity within 4 weeks of enrolment (day 1 visit) or with bicalutamide or nilutamide within 6 weeks of enrolment (day 1 visit) • History of prostate cancer progression on ketoconazole • Prior use, or participation in a clinical trial, of an investigational agent that blocks androgen synthesis or blocks the androgen receptor • Participation in a previous clinical trial of enzalutamide • Use of an investigational agent within 4 weeks of enrolment (day 1 visit)

		• Use of herbal products that may have hormonal antiprostate cancer activity and/or are known to decrease PSA levels or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrolment (day 1 visit) • Any condition or reason that, in the opinion of the investigator, interfered with the ability of the patient to participate in the trial, which placed the patient at undue risk, or complicates the interpretation of safety data

Source: PREVAIL Clinical Study Report2.
Abbreviations: ADT: androgen deprivation therapy; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CT: Computed Tomography; ECOG: Eastern Cooperative Oncology Group; GnRH: Gonadotropin releasing hormone; MRI: Magnetic Resonance Imaging; PCWG2: Prostate Cancer Clinical Trials Working Group; PSA: prostate specific antigen.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Both treatment arms were well balanced in terms of demographics, baseline disease characteristics and medical history2 (Table B8).

Patients in both arms had an ECOG of 0 (enzalutamide: 67.0%; placebo: 69.2%) or 1 (enzalutamide: 33.0%; placebo: 30.8%). In addition, the majority of patients had either medium (i.e., score of 5-7; enzalutamide: 48.6%; placebo: 46.8%) or high (i.e., score of 8-10; enzalutamide: 50.6%; placebo: 52.4%) Gleason score at diagnosis and had both, bone and soft tissue disease at time of screening (enzalutamide: 45.1%; placebo: 42.0%). In addition, 11.2% and 12.5% had visceral disease in the enzalutamide and placebo arms, respectively.

Table B8 Characteristics of participants in PREVAIL

PREVAIL	ENZA (N=872)	PLA (N=845)
Age (years)		
Mean	71.3 (8.51)	71.2 (8.42)
Median	72.0	71.0
Range	43.0, 93.0	42.0, 93.0
Race		
White	669 (76.7%)	655 (77.5%)
Black or African American	21 (2.4%)	13 (1.5%)
Asian	85 (9.7%)	82 (9.7%)
American Indian/Alaskan	1 (0.1%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	1 (0.1%)
Other	95 (10.9%)	94 (11.1)
Baseline ECOG performance		
0	584 (67.0%)	585 (69.2%)

PREVAIL	ENZA (N=872)	PLA (N=845)
1	288 (33.0%)	260 (30.8%)
2	0 (0.0%)	0 (0.0%)
PSA (ng/ml)		
Median	54.1	44.2
Range	0.1, 3182.0	0.3, 3637.0
Time (months) from Initial Diagnosis of Prostate Cancer to Randomisation		
Mean (SD)	78.6 (59.12)	76.2 (55.73)
Median	62.7	64.6
Gleason Score at Diagnosis		
2–4	7 (0.8%)	7 (0.9%)
5–7	407 (48.6%)	378 (46.8%)
8–10	424 (50.6%)	423 (52.4%)
Missing	34	37
Baseline use of corticosteroids > 7 days[a]	35 (4.0%)	36 (4.3%)
Disease Localisation at Screening		
Bone only	348 (39.9%)	335 (39.6%)
Soft tissue only	124 (14.2%)	149 (17.6%)
Both bone and soft tissue	393 (45.1%)	355 (42.0%)
None	7 (0.8%)	6 (0.7%)
Type of Disease Progression at Study Entry		
PSA progression only	375 (43.0%)	369 (43.7%)
Radiographic progression with PSA progression	349 (40.0%)	344 (40.7%)
Radiographic progression with no PSA progression	126 (14.4%)	107 (12.7%)
No disease progression per protocol	22 (2.5%)	25 (3.0%)
Measurable Soft Tissue Disease at Screening	396 (45.4%)	381 (45.1%)
Distribution of Disease at Screening		
Bone	741 (85.0%)	690 (81.7%)
Lymph node	437 (50.1%)	434 (51.4%)
Visceral disease (lung or liver)	98 (11.2%)	106 (12.5%)
Visceral liver	40 (4.6%)	34 (4.0%)
Visceral lung	64 (7.3%)	75 (8.9%)
Visceral lung and liver	6 (0.7%)	3 (0.4%)
Other soft tissue	113 (13.0%)	105 (12.4%)
Number of Bone Metastases at Screening		
0	131 (15.0%)	155 (18.3%)
1	97 (11.1%)	85 (10.1%)
2–4	213 (24.4%)	186 (22.0%)
5–9	146 (16.7%)	147 (17.4%)
10–20	140 (16.1%)	122 (14.4%)
> 20	145 (16.6%)	150 (17.8%)

Source: PREVAIL Clinical Study Report2
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ENZA: enzalutamide; PLA: placebo; PSA: prostate specific antigen; SD: Standard Deviation.
[a] Includes all steroid use for prostate cancer on the date of first dose of study drug and with continuous exposure for at least 7 days.

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The PREVAIL study examined two co-primary outcomes (OS and rPFS) and several secondary and exploratory outcomes. These are described in Table B9.

OS is the gold standard for oncology clinical studies. However, the PREVAIL study is set early in the treatment pathway of mHRPC patients and the majority of these patients would receive additional life-extending treatment after discontinuing the study treatment (enzalutamide or placebo). This is likely to dilute the OS data. Given the clinical relevance of rPFS and the fact that it is not influenced by subsequent treatment it was chosen as a co-primary endpoint. Radiographic PFS provides an accurate estimate of the treatment benefit of enzalutamide in these patients. PFS has been found to predict OS in prostate cancer patients[57,58]. In recent years, the use of rPFS in metastatic cancers as the primary endpoint has increased particularly in those cancers where the treatment benefit could be confounded by next lines of treatment[59].

Table B9 Primary, secondary and exploratory outcomes of PREVAIL

	Outcomes and measure	Definition of outcome	Reliability/validity/ current use in clinical practice
Primary outcomes (co-primary outcomes)	rPFS	Time from randomisation date to the first objective evidence of radiographic disease progression or death due to any cause within 168 days after treatment discontinuation,	PFS is not routinely used in clinical practice, but is a common endpoint assessed in oncology trials. Together with prolongation of OS and QoL improvement, delaying disease progression is the aim of treatment for mHRPC[66]. A substantial improvement in rPFS is clinically meaningful to mHRPC patients as it delays the time to

	Outcomes and measure	Definition of outcome	Reliability/validity/ current use in clinical practice
		whichever was first	increased tumour burden, which may ultimately lead to the decision to initiate opiates or cytotoxic chemotherapy.
	OS	Time from randomisation to death from any cause in the ITT population	OS is the gold standard recommended by EMA[60] and FDA[61,62] for clinical trials in advanced cancer. Prolongation of OS is the ultimate goal of therapies in advanced cancer[66].
Secondary endpoints	Time to first documented SRE	A SRE was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An alteration of analgesic medication for bone pain or the initiation of bisphosphonates or denosumab were not considered a SRE.	Prostate cancer most commonly metastasises to bone[12,63]. Together with pain, SREs are the most frequent symptoms associated with bone metastases[64] and are associated with high morbidity in these patients[65].
	Time to initiation of cytotoxic chemotherapy	Time from randomisation to the date of initiation of cytotoxic chemotherapy	No curative treatment for mHRPC is currently available. In mHRPC patients, chemotherapy is often delayed until the patient becomes symptomatic. Delaying initiation of chemotherapy and its associated toxicity without compromising the patient's QoL is in line with the objectives of the NHS Outcomes Framework[66].
	Time to PSA progression	PSA progression was defined according to the consensus guidelines of the PCWG2	PSA progression is frequently used in clinical practice to assess disease progression[31]
	PSA response (≥50% decrease)	PSA response was defined as a decrease in ≥50% according to PCWG2 criteria and compared with baseline values	PSA response is used in clinical practice as an indicator of how successful a treatment is[31]
	Best overall soft tissue response	Best overall soft tissue response was defined as complete	Although not always used in clinical practice, when assessed best overall soft tissue response is an indicator of

	Outcomes and measure	Definition of outcome	Reliability/validity/ current use in clinical practice
		or partial response on the basis of RECIST 1.1	how successful a treatment is[31]
	Safety	Safety was assessed based on occurrence of AEs, changes in the laboratory tests, ECG findings, and changes in physical examinations and vital signs	In clinical practice patients are regularly monitored for the tolerability of their treatment. In many cases, treatment needs to be interrupted or discontinued if side effects are severe.
Exploratory outcomes	Functional assessment of cancer therapy – prostate (FACT-P) response	Changes in the score during the study	QoL is not routinely assessed in clinical practice however, Astellas - Medivation proactively decided to include QoL given its relevance to all patients and in particular to oncology patients. Improved HRQL has been linked to better clinical outcomes in mHRPC in clinical trials. Enhancing the QoL of patients with cancer is the second domain of the NHS Outcomes Framework[66]
	Time to deterioration of the FACT-P	Deterioration was defined as a decrease in the score equal or higher than the minimal clinically important difference	QoL is not routinely assessed in clinical practice. However, improved HRQL has been linked to better clinical outcomes in mHRPC in clinical trials. Enhancing the QoL of patients with cancer is the second domain of the NHS Outcomes Framework[66] FACT-P consists of FACT-G and has a prostate cancer specific subscale. It has been used in several studies with patients with mHRPC[67].
	EQ-5D	Changes in the score during the study	EQ-5D is a standardised instrument for use as a measure of health outcome. It is not specific of prostate cancer or to any treatment. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care. EQ-5D complements other QoL measures such as FACT-P.
	Brief Pain Inventory (BPI)	Changes in the score during the study	Pain is frequently a manifestation of mHRPC, especially pain from bony metastases. The treatment of disease related pain is complicated, and often includes multiple medications, including a non-steroidal anti-inflammatory, short-acting opioid, and long-acting opioid.

	Outcomes and measure	Definition of outcome	Reliability/validity/ current use in clinical practice
			Even with complicated pain regimens, the result is often inadequate relief of pain. In addition, the treatment of pain is complicated by alterations in mental status, often severe constipation, and other side effects[12,31,68].
	Time to first post-baseline antineoplastic therapy	Antineoplastic therapy is defined as hormonal, cytotoxic or investigational treatment	Time to first post-baseline antineoplastic therapy is an indicator of disease progression
	PSA response ≥90%.	PSA response was defined as a decrease in ≥90% based on PCWG2 criteria and compared with baseline values	PSA response is used in clinical practice as an indicator of how successful a treatment is[31]

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken).

6.3.6.1 Hypothesis objective

The primary hypothesis was to test whether enzalutamide can prolong OS and/or rPFS in patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated compared to BSC2.

6.3.6.2 Patient populations used in the analyses

The intent-to-treat (ITT) population defined as all randomised patients was used for all efficacy analyses, and analyses of disposition, demographics, and baseline disease characteristics. Safety analyses were conducted using the Safety Population (all patients in the randomised population who received any study medication) and summarised by treatment group2.

6.3.6.3 Sample size, power calculation

The PREVAIL study was powered to evaluate OS and rPFS. The overall type I error rate (2-sided) for the study was 0.05 with 0.049 allocated to OS and 0.001 allocated to rPFS2.

The sample size considerations for the OS outcome were based on the following2:

- 1:1 randomisation ratio between the 2 treatment groups (enzalutamide and placebo)
- A target hazard ratio (HR) for OS of 0.815. The expected median OS for the placebo group was 28 months as measured from the date of first randomisation. A target HR of 0.815 corresponded to a 22.7% increase in median OS for the enzalutamide group compared with the placebo group (34.4 months vs 28 months)
- A minimum of 765 deaths was to provide 80% power to detect the target HR based on a 2-sided log-rank test and an overall significance level of 0.049
- Up to 2 analyses were planned for OS including an interim analysis at approximately 516 deaths and a final analysis after a minimum of 765 deaths. A 2-stage group sequential design with Lan-DeMets alpha spending function with an implementation of O'Brien-Fleming stopping boundaries was used to preserve the overall alpha for OS at the 0.049 level (2-sided). If the number of deaths for the interim analysis did not correspond to the projected number of deaths, alpha spending between the 2 OS analyses was to be adjusted accordingly based upon 765 total events, and the overall alpha for OS was to be preserved at the 0.049 level (2-sided).

The co-primary analysis of rPFS was determined based on the following considerations2:

- A target HR of 0.57. The expected median rPFS for the placebo group was 8 months as measured from the date of randomisation. A target HR of 0.57 corresponded to a 75% increase in median rPFS for the enzalutamide group compared with the placebo group (14 months vs 8 months).
- A targeted minimum of 410 rPFS events was to provide ≥99% power to detect a target HR of 0.57 based on a 2-sided log-rank test and a significance level of 0.001.

The study planned to randomise approximately 1680 patients (840 patients per treatment group) in order to observe at least 765 deaths due to any cause. This sample size included a 10% increase adjustment for patients lost to follow-up.

6.3.6.4 Handling of missing data

Missing data were not imputed unless otherwise specified.

For the OS analysis, partial death dates or censoring dates (last date known alive) for determination of the duration of OS were imputed using the following rules: missing month and day imputed as 15 January, missing day imputed as the 15th day of the month, and completely missing dates were not imputed2.

Missing scan data for the rPFS assessment by the independent review facility were summarised by frequency and percentage of scans received and missing by treatment group, by scan modality (CT/MRI or radionuclide bone scan), and by visit.

The percentage of received and missing scans was calculated based on the expected number of scans by visit2.

For the primary analysis of the FACT-P, EQ-5D and BPI, the mixed model repeated measures model (MMRM) which assumes that missingness is at random (MAR) was used. That is, MMRM assumes that, given the statistical model and given the observed values of the outcome, missingness is independent of the unobserved values. A corollary is that MAR assumes that a subject's missing values can be estimated based on similar subjects who remained in the study. This infers that withdrawals (who may not receive study medication) have similar symptoms to some who continue to be treated. In addition, as recommended by the U.S. NRC report on missing data (page 10)[69] and the EU Guidance on missing data (page 12)[70], a model that assumes missing not at random (MNAR) was used in a sensitivity analysis, to assess the robustness of the primary estimate with regard to missing data, when the MAR assumption is replaced by assumptions that are likely to be relatively less favourable to the experimental treatment[53].

For safety analyses missing the day of the month (for determination of the last dose of study drug or the first cytotoxic chemotherapy or new investigational agent for prostate cancer), the 15th of the month was used to impute the missing data to determine the treatment-emergent period2.

6.3.6.5 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The co-primary endpoints (OS and rPFS) were examined in several patient subgroups that had been pre-specified in the study protocol on the basis of being accepted prognostic factors for prostate cancer, demographic features of interest, or represent different regional practice patterns:

- ECOG performance status at study entry (0 vs 1)
- Age (<75 vs ≥75)
- Geographic region (North America vs Europe vs rest of the world)
- Gleason Score at diagnosis (≤7 vs ≥8)
- Type of progression at study entry (PSA progression only vs radiographic progression with or without PSA progression)
- Visceral disease at study entry (yes vs no)
- Baseline PSA value (≤ median vs > median)
- Baseline lactate dehydrogenase (LDH) value (≤ median vs > median)
- Baseline haemoglobin value (≤ median vs > median).

6.3.6.6 Post-hoc analyses

In addition to the endpoints listed above, a post-hoc analysis on the time to treatment discontinuation (TTD) was conducted. This analysis was done because TTD was deemed relevant for the health economic model (section 7.3.1). In addition, a post-hoc adjustment of OS data was also conducted to take into account any post-study

treatment received 2nd line by patients that differed from the treatment these patients would have received in clinical practice. OS adjustment was also performed for modelling purposes.

Time to treatment discontinuation

The TTD endpoint was assessed for modelling purposes as this was considered a more accurate reflection of what happens to mHRPC patients in clinical practice, and is aligned with what has previously been accepted by NICE[32]. Clinicians consider that TTD reflects more accurately treatment duration in clinical practice than rPFS9.

In PREVAIL, the decision to discontinue treatment was based on a combination of criteria: confirmed radiographic disease progression or a SRE, and the initiation of cytotoxic chemotherapy or an investigational agent for treatment of prostate cancer. In addition, the occurrence of an AE, where continued administration of study drug was deemed not in the patient's best interest by the Investigator and/or the Sponsor, also resulted in the removal of the patient from therapy.

For the TTD analysis, patients who had not discontinued treatment at the time of data cut-off (16 September 2013) were censored.

Overall survival adjustment

In PREVAIL, patients could receive any approved or investigational subsequent antineoplastic therapies after discontinuation of study drug. Such therapies included docetaxel, which is indicated as first line treatment in the UK treatment pathway [31], hormonal treatments indicated in this or earlier disease stage, and also abiraterone, enzalutamide, cabazitaxel and sipuleucel-T, which are currently not included at this stage of the UK treatment pathway[31]. In addition, after unblinding of the study, all patients were offered enzalutamide in an open-label study. Overall, in PREVAIL [redacted] patients [redacted] in the placebo arm and [redacted] patients [redacted] in the enzalutamide arm received a 2nd line treatment that differed from the treatment patients would have received in clinical practice[31].

The standard ITT analysis, i.e. all randomised patients, is likely to underestimate the ''true'' OS benefit associated with the study drug when patients switch and benefit from treatments outside of the treatment pathway, and will affect the cost-effectiveness analyses which make use of the OS evidence[71]. Methods to correct for such treatment switching are discussed in the NICE DSU technical support document 16. There are two groups of statistical methods to correct for such treatment switching[72]: naïve or simple methods and complex methods; NICE recommends to avoid naïve methods. Available complex methods can be classified as 'randomisation-based' methods - such as the rank preserving structural failure time model (RPSFTM) or iterative parameter estimation algorithm (IPE) - and 'observational-based' methods - such as two stage method or inverse probability of censoring weights (IPCW).

The optimal method to control for switching in survival analysis remains an area of academic debate and all approaches have their strengths and limitations. Simulation studies have shown that the different methods can be expected to produce different levels of bias depending upon the scenario in which they are applied[71,72,73]. Whilst all complex methods produce low bias in some scenarios, and can be expected to

produce lower bias than a standard ITT analysis in most cases, each are sensitive to specific factors – for instance the RPSFTM and IPE methods are prone to bias when the "common treatment effect" assumption does not hold, and the IPCW is volatile when switching proportions are very high and sample sizes are small. Hence, method selection is of key importance. As recommended by the NICE DSU technical support document 16[72], we have examined the trial characteristics and treatment switching mechanism in order to assess which switching adjustment method is likely to be most appropriate in PREVAIL. The reasons behind the selection of the methods used are summarised below and detailed in the OS adjustment report[37].

RPSFTM and IPE methods are designed to cope with treatment switching in either direction (provided the control treatment is placebo, or non-active treatment), but are not suitable when switching is to a third treatment[72]. In such circumstances a multi-parameter RPSFTM would be required, but these have been shown to perform poorly in practice[74,75,76]. In PREVAIL, patients in both arms of the trial switched on to several different treatments after the study drug was discontinued. Hence, to adjust for these switchers, we cannot use RPSFTM or IPE methods. By contrast, observational-based methods, like the IPCW and two-stage methods, can be adapted to adjust for switching in any direction to any treatment, with models being applied to different groups as appropriate[71]. We have selected therefore the IPCW and the two stage methods as the methods suitable for adjustment of PREVAIL OS data.

A full statistical description of the IPCW and two stage methods is included in the OS adjustment report[37]. A non-technical description of the methodological approach is presented below. The analyses were conducted in consultation with a leading expert in applying these methods.

Inverse probability of censoring weights (IPCW) analysis

The IPCW method involves censoring patients upon treatment switch, and then controlling for this potentially informative censoring by weighting the follow-up information for patients who remain at risk for the event such that they account not only for themselves, but also for patients with similar characteristics (both baseline and time-dependent) whose follow-up was censored by informative censoring[77].

It has previously been acknowledged that IPCW can be a valid option to correct for switching bias[78,79,80]. A very important limitation of the method is its reliance on the "no unmeasured confounders" assumption, that is data must be available on all baseline and time dependent prognostic factors for mortality that independently predict informative censoring (switching).

In the context of PREVAIL, the IPCW analysis consisted of three steps as follows:

1. *Create Panel Data*: For each patient, follow-up time from randomisation until treatment switch or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into intervals based on visits dates. In PREVAIL, visits were scheduled every four weeks until week 49 and every 12 weeks thereafter. For each of these intervals, time-dependent variables that might be predictive of switching and mortality (e.g. ECOG performance status, PSA level, LDH laboratory level, history of grade 3/4/5 AEs since randomisation, occurrence of grade 3/4 AEs, corticosteroid use, EQ-5D utility index, FACT-P total score, and time since the date of study treatment discontinuation) were calculated.

2. *Calculated Stabilised Weights:* Using the panel data created in the Step 1, for each patient (i) and interval (j), stabilised weights, SWi (j), were estimated. The denominator of the weights is the probability of remaining uncensored (i.e. not switching) to the end of interval (j) given baseline and time-dependent confounders. The numerator of the weights is the probability of remaining uncensored to the end of interval (j) given only baseline confounders. Estimates were obtained by fitting pooled logistic models with censoring (switching) as the dependent variable.
3. *Run IPCW Cox Regression*: A HR for OS was estimated using a weighted Cox proportional hazard regression model, where patient intervals were weighted by the stabilised weights calculated in Step 2. In this model, patients who switched treatment were censored at that date. Because even robust standard errors (SEs) for the HRs obtained from the Cox regression analysis do not account for the variability associated with the estimation of the stabilised weights, 95% confidence intervals for HR estimates were obtained by bootstrapping. A 95% CI for the HR was estimated based on the 2.5 and 97.5 percentiles of 1000 bootstrap replicates.

Two stage method analysis

The two stage method involves first estimating a treatment effect specific to switching patients and then using this to derive a counterfactual dataset unaffected by switching[71]. This method also relies upon the "no unmeasured confounders" assumption, but only at the point of disease event. Additional key limitations are:

- It can only be applied if an appropriate secondary baseline exists,
- Unless all switching occurs soon after the secondary baseline time-point, it will be prone to time-dependent confounding.

To our knowledge, the two stage method has not yet been used in a published HTA.

In the context of PREVAIL, the two stage method analysis consisted of four steps as follows:

1. *Create Observational Datasets*: For each patient, a secondary baseline was defined as the treatment discontinuation date for both switchers and non-switchers. In PREVAIL, both treatment arms included switchers. Thus, data from the secondary baseline onwards are considered as two separate observational datasets – one for the placebo arm, and one for the enzalutamide arm.
2. *Acceleration Factors (AF) and counterfactual survival time calculation*: Two accelerated failure time (AFT) models, e.g. Weibull and a Generalised Gamma, were fitted separately to the two observational datasets. The models included a covariate for switching, prognostic covariates measured at secondary baseline (or the last assessment before the secondary baseline) and relevant covariates measured at study baseline, i.e. the beginning of the study. The AFs were calculated as the exponential of the coefficient associated with the switching indicator for each treatment group separately. The AFs obtained were used to shrink the survival time for switchers (both events and censor) in each treatment group. Counterfactual survival time is calculated as:

Counterfactual survival time = Time from start of randomised drug to treatment discontinuation + Time from treatment discontinuation to death or censoring / AF

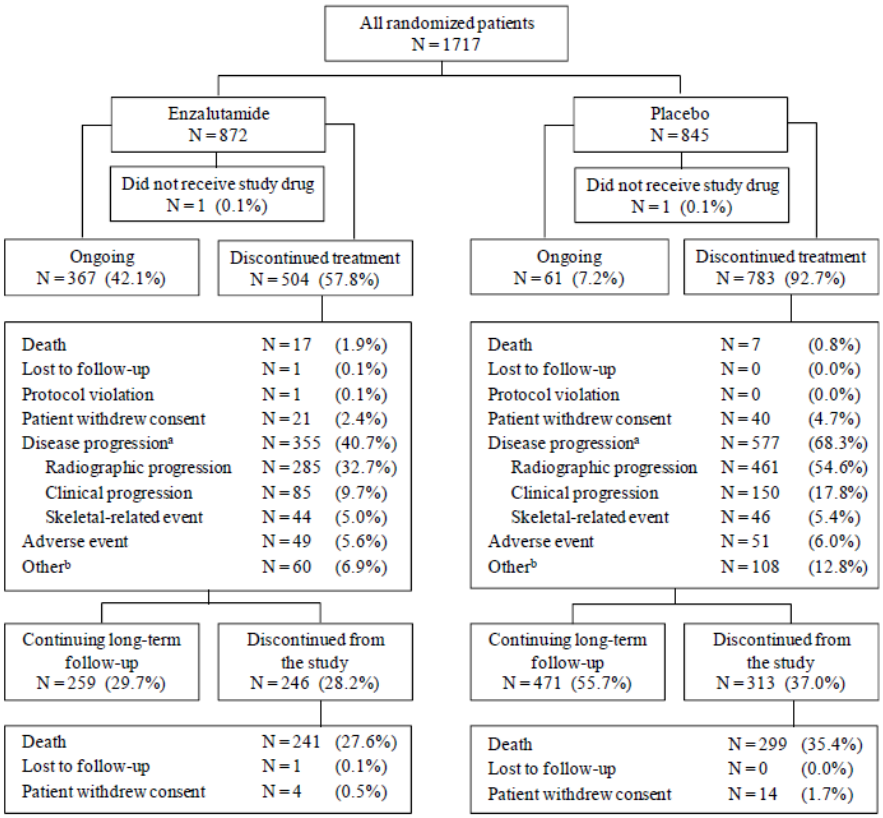
3. *Recensoring*: Recensoring time was calculated for all patients as initial censoring time divided by the acceleration factor. Survival times, observed or counterfactual, for all patients were further adjusted to be equal to either the survival time (shrunk or observed) or the potential recensoring time if it occurred earlier.
4. *Run Cox regression*: A HR was obtained from a Cox regression model with treatment as the only covariate. Standard Errors (SE) for HRs were calculated by means of bootstrapping. A 95% CI for the HR was estimated based on the 2.5 and 97.5 percentiles of 1000 bootstrap replicates.

Participant flow

6.3.7 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The ITT set in PREVAIL consisted of 1,717 patients (enzalutamide: N=872; placebo: N=845). Of these patients 1,715 received at least one dose of enzalutamide (N=871) or placebo (N=844) and constituted the safety population (Figure B2). The number of patients included in each of the analyses presented here are provided in Table B10.

Figure B2 Patient disposition flowchart as of 16 Sep 2013 (ITT Population)



Source: PREVAIL Clinical Study Report2
Abbreviations: ITT, intent-to-treat.
Percentages are based on total number of randomised patients in each treatment group and overall.
[a] Patients discontinued due to disease progression could be counted in more than 1 subcategory.
[b] The most common reason was rising prostate-specific antigen.

Table B10 Analysis sets in PREVAIL

Analysis population	ENZA (N=872)	PLA (N=845)
Randomised (ITT Population)	872 (100%)	845 (100%)
Not treated with study drug	1 (0.0%)	1 (0.0%)
Evaluable for rPFS	832 (95.4%)	801 (94.8%)
Evaluable for PSA response	854 (97.9%)	777 (92.0%)
Evaluable for best overall soft tissue response	396 (45.4%)	381 (45.1%)
Evaluable for pain progression	698 (80.0%)	358 (42.4%)
Safety Population	871 (100%)	844 (100%)

Source: PREVAIL Clinical Study Report2
Abbreviations: ENZA: enzalutamide; ITT: intent-to-treat; PLA: placebo; PSA: prostate specific antigen; rPFS: radiographic progression free survival.

Patients continued treatment with the study drug until confirmed radiographic disease progression or a SRE, and the initiation of cytotoxic chemotherapy or an investigational agent for treatment of prostate cancer. The mean and median treatment duration were higher in the enzalutamide arm (15.8 and 16.6 months, respectively) than in the placebo arm (7.0 and 4.6 months, respectively)2.

Overall, 367 (42.1%) patients in the enzalutamide arm and 61 (7.2%) patients in the placebo arm remained on study drug as of the interim OS data cut-off date (Table B11). The most commonly reported reason for study drug discontinuation in both arms was disease progression (enzalutamide: 40.7%; placebo: 68.3%). Adverse events was the reason of study drug discontinuation in 5.6% and 6.0% of patients in the enzalutamide and placebo arms, respectively.

Table B11 Patient disposition at interim analysis (16 Sep 2013; ITT)

Study Treatment Disposition	ENZA (N=872)	PLA (N=845)
Ongoing treatment (at data cut-off date)	367 (42.1%)	61 (7.2%)
Treatment discontinued	504 (57.8%)	783 (92.7%)
Did not receive study treatment	1 (0.1%)	1 (0.1%)
Primary Reason for Study Drug Discontinuation		
Death	17 (1.9%)	7 (0.8%)
Lost to follow-up	1 (0.1%)	0 (0.0%)
Protocol violation	1 (0.1%)	0 (0.0%)
Withdrawal consent	21 (2.4%)	40 (4.7%)
Disease progression	355 (40.7%)	577 (68.3%)
Radiographic progression[a]	285 (32.7%)	461 (54.6%)
Clinical progression[a]	85 (9.7%)	150 (17.8%)
Skeletal-related event[a]	44 (5.0%)	46 (5.4%)
Adverse event	49 (5.6%)	51 (6.0%)
Other	60 (6.9%)	108 (12.8%)
Primary Reason for Discontinuation of Study		
Death	241 (27.6%)	299 (35.4%)
Lost to follow-up	1 (0.1%)	0 (0.0%)
Withdrew consent to be followed	4 (0.5%)	14 (1.7%)
Sponsor decision	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)

Source: PREVAIL Clinical Study Report2
Abbreviations: ENZA: enzalutamide; PLA: placebo.
[a]Patients could have more than 1 type of disease progression, but could only be counted once for the summary of disease progression.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

PREVAIL is a randomised double-blind placebo-controlled international study (N=1,717). Patients were assigned to treatment using a centrally administered, randomised, permuted-block method and stratified by study site. An interactive voice/web response system (IVRS/IWRS) assigned the patient a study drug bottle number according to the randomisation code on day 12.

The study included an independent data monitoring committee that monitored and reviewed safety data on an ongoing basis2.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

A detailed quality assessment of PREVAIL is provided in appendix 3, section 10.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

The quality assessment of PREVAIL is provided in Table B12.

Table B12 Quality assessment results for RCTs

	PREVAIL
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis,

the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.

- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

6.5.3.1 Co-primary efficacy outcome – OS

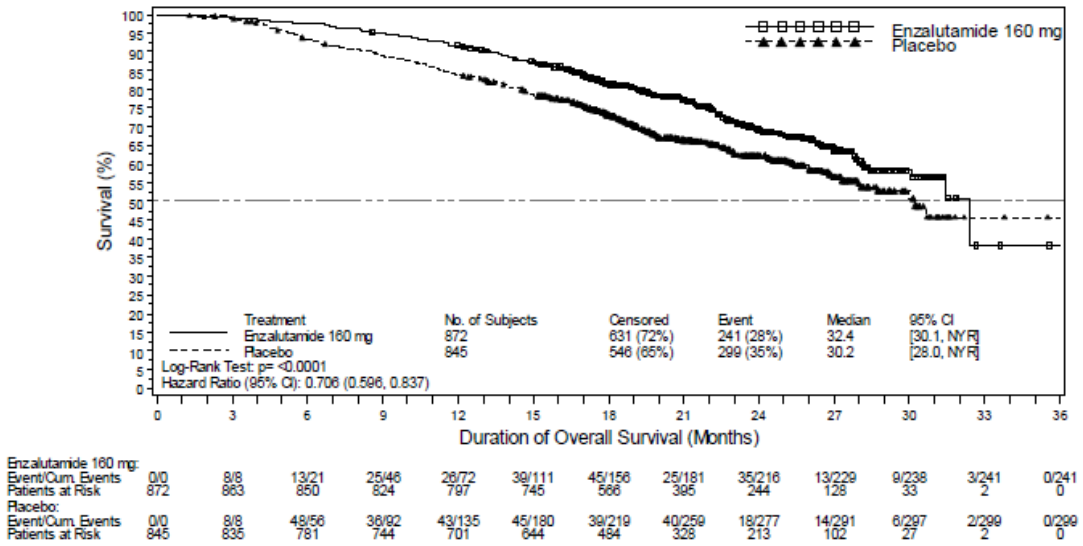
A prespecified interim analysis of OS was planned when approximately 516 deaths (or 67% of the total number of deaths for the final analysis) had occurred. The preplanned interim analysis of OS was prepared by an independent statistical unit, and presented by the independent statistician to the independent DMC during the closed session on 21 Oct 2013. Based on these analyses, the DMC recommended halting the blinded portion of the study and allowing patients randomised to placebo access to open-label enzalutamide.

The interim analysis of OS was therefore considered the final analysis and no further analyses of this endpoint were planned. The treatment-level blind was maintained for study sites, patients, and the sponsors, until the lock of the blinded database on 03 Dec 2013. However, for modelling purposes an additional data cut-off was conducted on 30 June 2014. The outcomes of this analysis are also presented here.

At the time of interim analysis (16 September 2013), 241 deaths had occurred among patients in the enzalutamide arm and 299 deaths among patients in the placebo arm (Figure B3).

In the protocol pre-specified interim analysis (median follow-up of 22.2 and 22.4 months in the enzalutamide and placebo arms, respectively), median OS was 32.4 months (95% CI: [30.1; not yet reached]) with enzalutamide and 30.2 months (95% CI: [28.0; not yet reached]) with placebo[2,3]. Enzalutamide significantly reduced the risk of mortality by 29% compared to placebo (unstratified HR: 0.706; 95% CI: [0.596, 0.837]; p<0.0001).

Figure B3 Kaplan-Meier curve for OS (16 September 2013; ITT)



Source: PREVAIL Clinical Study Report[2]

Superiority of enzalutamide over placebo was also observed in the most mature data cut-off (30 June 2014) with 775 events (Table B13). Median OS was 33.51 and 30.98 months for enzalutamide and placebo, respectively. Compared with placebo, enzalutamide reduced the risk of death by [redacted]

Table B13 Median OS (30 June 2014; ITT)

	ENZA (N=872)	PLA (N=845)
Duration of OS (months)		
Number of subjects with events	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Unstratified Analysis		
Hazard ratio (95% CI)[d]	[redacted]	
P-value (log-rank)	[redacted]	

Source: Report for OS adjustment[37]

Enzalutamide significantly prolonged OS compared to placebo despite a higher proportion of patients in the placebo arm being switched to therapies outside of UK clinical practice, some of which may have had the potential to prolong survival after discontinuation of the trial medication. Median OS at all data cut-off analyses includes OS of patients who received post-study treatment. The median OS presented in this section is not adjusted for post-study treatment. As shown in the OS adjustment analyses presented in section 6.3.6.6, unadjusted OS underestimates the OS benefit of enzalutamide over placebo.

The proportion of patients on the different post-baseline antineoplastic therapies with demonstrated OS benefit at the 16 September 2013 cut-off are indicated in Table B14. Overall, 43.8% (N=382) and 76.0% (N=642) of patients in the enzalutamide and placebo arms respectively were given at least one post-baseline antineoplastic therapy, and 40.3% (N=351) and 70.3% (N=594), respectively at least one post-baseline antineoplastic therapy with demonstrated OS benefit at the September data cut-off. Patients could receive these therapies as second or subsequent lines of treatment. In contrast, data provided in Table B23 corresponds to second-line therapy only.

Table B14 Subsequent therapies to treat prostate cancer used in ≥10% of patients in any arm (16 September 2013; ITT)

Post-baseline antineoplastic therapy use	ENZA (N=872)	PLA (N=845)
Patients taking any post-baseline antineoplastic therapy	382 (43.8%)	642 (76.0%)
Patients taking any of the following post-baseline antineoplastic therapies with demonstrated OS benefit	351 (40.3%)	594 (70.3%)
Docetaxel	286 (32.8%)	479 (56.7%)
Abiraterone acetate[a]	179 (20.5%)	385 (45.6%)
Cabazitaxel	51 (5.8%)	110 (13.0%)
Sipuleucel-T	12 (1.4%)	10 (1.2%)
Enzalutamide	9 (1.0%)	37 (4.4%)

Source: PREVAIL Clinical Study Report2
Abbreviations: ENZA: enzalutamide; PLA: placebo.
[a] Concomitant use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a SRE. However, only 7 (0.8%) patients received concomitant abiraterone.

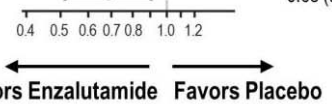
Overall survival was examined in several patient subgroups that had been pre-specified in the study protocol on the basis of being accepted prognostic factors for prostate cancer, demographic features of interest, or represent different regional practice patterns (Figure B4):

- ECOG performance status at study entry (0 vs 1)
- Age (<75 vs ≥75)
- Geographic region (North America vs Europe vs rest of the world)
- Gleason Score at diagnosis (≤7 vs ≥8)
- Type of progression at study entry (PSA progression only vs radiographic progression with or without PSA progression)
- Visceral disease at study entry (yes vs no)
- Baseline PSA value (≤ median vs > median)
- Baseline lactate dehydrogenase (LDH) value (≤ median vs > median)
- Baseline haemoglobin value (≤ median vs > median).

Median OS in all patient subgroups favoured enzalutamide over placebo including more difficult-to-treat patient subsets such as patients over 75 years old, patients with visceral disease, and patients with radiographic progression at screening.

Figure B4 Subgroup analyses of overall survival

Subgroup	No. of Patients Enzalutamide/ Placebo	Overall Survival Median (mo) Enzalutamide/ Placebo	Hazard Ratio for Death (95% CI) (Unstratified)
All patients	872/845	32.4/30.2	0.71 (0.60–0.84)
ECOG performance status at baseline=0	584/585	32.4/NYR	0.70 (0.56–0.87)
ECOG performance status at baseline=1	288/260	27.9/26.9	0.69 (0.53–0.90)
Age <75 yr	555/553	31.5/NYR	0.77 (0.62–0.96)
Age ≥75 yr	317/292	32.4/25.1	0.60 (0.47–0.79)
Geographic region – North America	218/208	32.4/NYR	0.83 (0.60–1.16)
Geographic region – Europe	465/446	NYR/28.0	0.68 (0.54–0.86)
Geographic region – Rest of world	189/191	NYR/28.7	0.62 (0.42–0.92)
Total Gleason Score at diagnosis ≤7	414/385	NYR/30.0	0.66 (0.51–0.85)
Total Gleason Score at diagnosis ≥8	424/423	31.5/30.2	0.77 (0.60–0.97)
Type of progression at study entry – PSA progression only	375/369	NYR/NYR	0.60 (0.45–0.82)
Type of progression at study entry – Radiographic progression with or without PSA progression	475/451	30.1/27.3	0.75 (0.61–0.92)
Visceral disease (lung and/or liver) at screening – Yes	98/106	27.8/22.8	0.82 (0.55–1.23)
Visceral disease (lung and/or liver) at screening – No	774/739	NYR/30.2	0.69 (0.57–0.83)
Baseline PSA value (ng/mL) ≤median (49.60)	420/440	NYR/NYR	0.78 (0.58–1.05)
Baseline PSA value (ng/mL) >median (49.60)	452/404	28.0/23.0	0.61 (0.49–0.75)
Baseline LDH value (U/L) ≤median (185)	443/423	NYR/NYR	0.57 (0.43–0.76)
Baseline LDH value (U/L) >median (185)	428/421	30.1/26.0	0.80 (0.65–0.99)
Baseline hemoglobin value (g/L) ≤median (130)	455/416	28.4/24.5	0.69 (0.55–0.85)
Baseline hemoglobin value (g/L) >median (130)	417/429	NYR/NYR	0.68 (0.52–0.91)



Source: Beer et al[3]

6.5.3.2 Co-primary efficacy outcome – rPFS

The primary analysis of rPFS was pre-specified based on at least the first 410 centrally determined rPFS events observed. The data cut-off date for the primary rPFS analysis was 06 May 2012, at which time 439 centrally determined rPFS events (enzalutamide: N=118, 14.2%; placebo: N=321, 40.1%) were reported2. Patients randomised after the data cut-off date (N=84) were not included in the analysis2.

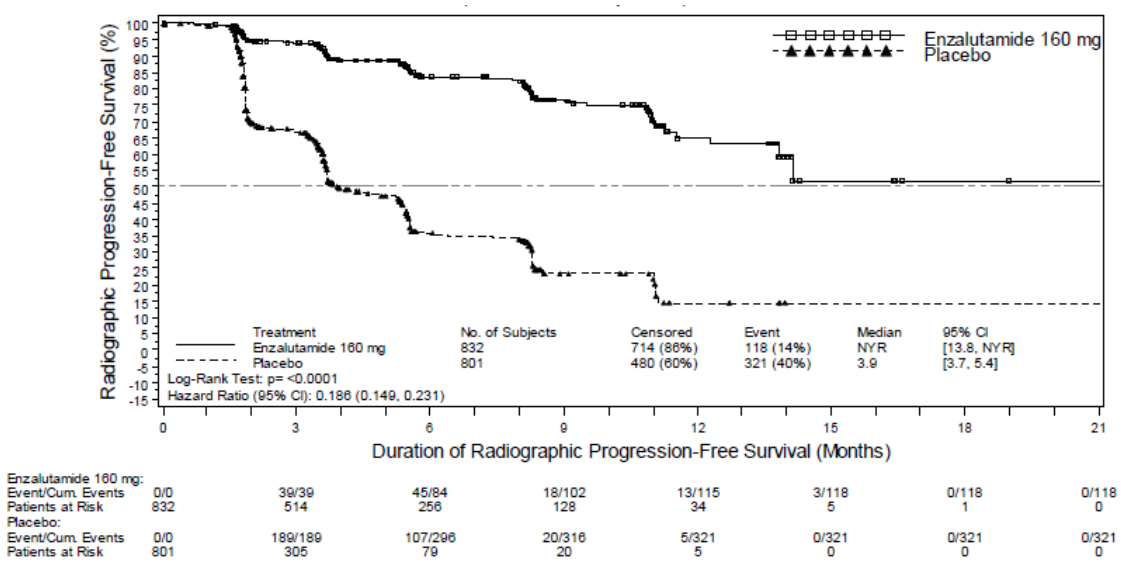
Median follow-up times based on reverse Kaplan-Meier estimation were 5.4 months for the enzalutamide group and 3.6 months for the placebo group (Table B15). Treatment with enzalutamide resulted in a statistically significant reduction in risk of radiographic progression (as determined by central review) or death compared with treatment with placebo with a hazard ratio of 0.186 (95% CI: [0.149, 0.231], p<0.0001). The median time to an rPFS event was not yet reached in the enzalutamide group versus 3.9 months in the placebo group. The Kaplan-Meier curves of rPFS are provided in Figure B5.

Table B15 Median rPFS (06 May 2012; ITT)

	ENZA (N=832)	**PLA (N=801)**
Status of rPFS Survival Follow up		
Events[a]	118 (14.2%)	321 (40.1%)
Radiographic progression	105 (12.6%)	295 (36.8%)
Death without documented radiographic progression	13 (1.6%)	26 (3.2%)
Censored[b]	714 (85.8%)	480 (59.9%)
Duration of rPFS (months)[b,c]		
Censored	714 (85.8%)	480 (59.9%)
25% percentile	9.5	1.9
Median (95% CI)	NYR (13.8, NYR)	3.9 (3.7, 5.4)
75% percentile	NYR	8.3
Unstratified Analysis		
Hazard ratio (95% CI)[d]	0.186 [0.149, 0.231]	
P-value (log-rank)	p<0.0001	

Source: PREVAIL Clinical Study Report2
Abbreviations: CI: confidence interval; ENZA: enzalutamide; ITT: intent-to-treat; PLA: placebo; rPFS: radiographic progression-free survival.
Patients randomised after the May 2012 cut-off date are not included in the analysis.
a Based on the earliest contributing event (radiographic progression or death due to any cause within 168 days after treatment discontinuation).
b Patients who were not known to have had an rPFS event at the time of analysis data cut-off are censored at date of last assessment showing no objective evidence of radiographic progression prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, skeletal-related event, treatment discontinuation and 2 or more consecutive missed tumour assessments.
c Based on Kaplan-Meier estimates.
d The hazard ratio is based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide.

Figure B5 Kaplan-Meier curve for rPFS as assessed by independent central review (ITT)



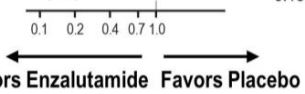
Enzalutamide 160 mg:								
Event/Cum. Events	0/0	39/39	45/84	18/102	13/115	3/118	0/118	0/118
Patients at Risk	832	514	256	128	34	5	1	0
Placebo:								
Event/Cum. Events	0/0	189/189	107/296	20/316	5/321	0/321	0/321	0/321
Patients at Risk	801	305	79	20	5	0	0	0

Source: PREVAIL Clinical Study Report2

Radiographic PFS was also examined in the same patient subgroups pre-specified in the study protocol as for OS. Median rPFS in all these patient subgroups favoured enzalutamide over placebo2 (Figure B6).

Figure B6 Subgroup analyses of rPFS

Subgroup	No. of Patients Enzalutamide/ Placebo	rPFS Median (mo) Enzalutamide/ Placebo	Hazard Ratio for rPFS (95% CI) (Unstratified)
All patients	832/801	NYR/3.9	0.19 (0.15–0.23)
ECOG performance status at baseline=0	557/549	NYR/3.7	0.15 (0.11–0.20)
ECOG performance status at baseline=1	275/252	14.1/4.0	0.27 (0.19–0.37)
Age <75 yr	529/517	NYR/4.6	0.20 (0.15–0.26)
Age ≥75 yr	303/284	NYR/3.7	0.17 (0.12–0.24)
Geographic region – North America	214/204	NYR/4.8	0.17 (0.12–0.25)
Geographic region – Europe	456/435	13.8/3.8	0.21 (0.15–0.28)
Geographic region – Rest of world	162/162	NYR/3.7	0.14 (0.08–0.25)
Total Gleason Score at diagnosis ≤7	401/370	14.1/5.3	0.16 (0.11–0.22)
Total Gleason Score at diagnosis ≥8	399/394	NYR/3.7	0.23 (0.17–0.31)
Type of progression at study entry – PSA progression only	348/341	NYR/5.6	0.16 (0.11–0.24)
Type of progression at study entry – Radiographic progression with or without PSA progression	464/435	14.1/3.7	0.18 (0.14–0.24)
Visceral disease (lung and/or liver) at screening – Yes	97/101	NYR/3.6	0.28 (0.16–0.49)
Visceral disease (lung and/or liver) at screening – No	735/700	14.1/4.0	0.17 (0.14–0.22)
Baseline PSA value (ng/mL) ≤median (51.10)	395/411	NYR/5.5	0.16 (0.11–0.23)
Baseline PSA value (ng/mL) >median (51.10)	437/389	13.8/3.6	0.18 (0.14–0.24)
Baseline LDH value (U/L) ≤median (185)	427/402	14.1/4.0	0.14 (0.10–0.20)
Baseline LDH value (U/L) >median (185)	404/398	NYR/3.8	0.23 (0.17–0.31)
Baseline hemoglobin value (g/L) ≤median (130)	429/388	14.1/3.7	0.24 (0.18–0.31)
Baseline hemoglobin value (g/L) >median (130)	403/413	NYR/5.3	0.13 (0.09–0.19)
Baseline bisphosphonate or denosumab use – Yes	215/222	13.8/5.6	0.27 (0.18–0.41)
Baseline bisphosphonate or denosumab use – No	617/579	NYR/3.7	0.16 (0.12–0.21)



Source: Beer et al[3]

Sensitivity analyses of rPFS using various censoring rules, such as inclusion of all deaths rather than deaths within 168 days of treatment discontinuation, requirement for soft tissue confirmation before week 13, and other analyses censoring for clinical progression events also confirmed the primary analysis of median rPFS. The hazard ratios for the different rPFS sensitivity analyses ranged from 0.174-0.234, all p<0.00012 (Table B16).

Regarding the sensitivity analyses, rPFS using investigator assessments of radiographic progression were consistent with the primary analysis of rPFS (central review), irrespective of the data cut-off date used (06 May 2012, i.e., the rPFS data cut-off date, or 16 September 2013, i.e., the interim OS data cut-off date). Given the larger number of patients included in the analysis at the 16 September 2013 data cut-off date, these are the data included in the economic model (sensitivity analysis 6 in Table B16). At this data cut-off, rPFS as assessed by the investigator was 19.0 months (95% CI: [18.1, 22.3]) and 5.4 months (95% CI: [4.2, 5.6]) for enzalutamide and placebo groups, respectively.

Table B16 Summary of sensitivity analysis of the duration of rPFS (ITT)

	Enzalutamide	**Placebo**
Primary analysis from central review		
Events	118 (14.2%)	321 (40.1%)
Hazard ratio (95% CI)	0.186 (0.149, 0.231)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 1 Based on investigator review		
Events	117 (14.1%)	296 (37.0%)
Hazard ratio (95% CI)	0.219 (0.176, 0.273)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 2 Included all deaths during cut-off rather than only deaths within 168 days of treatment discontinuation		
Events	121 (14.5%)	326 (40.7%)
Hazard ratio (95% CI)	0.186 (0.150, 0.231)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 3 Considered new SREs, any radiation therapy for prostate cancer, or new antineoplastic therapy as rPFS events		
Events	171 (20.6%)	450 (56.2%)
Hazard ratio (95% CI)	0.184 (0.153, 0.221)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 4 Considered the date of the next scheduled visit as the date of progression if progression was determined at an unscheduled visit		
Events	118 (14.2%)	321 (40.1%)
Hazard ratio (95% CI)	0.185 (0.149, 0.231)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 5 Required confirmation of soft tissue progression before week 13		
Events	108 (13.0%)	245 (30.6%)
Hazard ratio (95% CI)	0.234 (0.186, 0.296)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 6 Based on investigator assessments		

	Enzalutamide	Placebo
using cut-off date of interim OS (16 September 2013)		
N	872	845
Events	387 (44.4%)	502 (59.4%)
Hazard ratio (95% CI)	0.307 (0.267, 0.353)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 7 Considered patients discontinuing for clinical progression as rPFS events		
Events	128 (15.4%)	354 (44.2%)
Hazard ratio (95% CI)	0.178 (0.144, 0.220)	
Log-rank test p-value	<0.0001	
Sensitivity Analysis 8 Considered patients discontinuing treatment for any reason as rPFS events		
Events	178 (21.4%)	480 (59.9%)
Hazard ratio (95% CI)	0.174 (0.146, 0.209)	
Log-rank test p-value	<0.0001	

Source: PREVAIL Clinical Study report2

6.5.3.3 Secondary and exploratory outcomes

Results for secondary and exploratory parameters are not differentiated in this section. In addition, and to ease the reading, for certain endpoints (e.g., those related to PSA response) all results (secondary and exploratory) are provided together.

Unless specified otherwise, all data provided in this section corresponds to the data cut-off date of 16 September 2013.

Time to first SRE

In PREVAIL, 31.9% (N=278) of patients in the enzalutamide arm and 36.6% (N=309) of patients in the placebo arm experienced SREs during the study (Table B17). Among patients with SREs, the most commonly reported SRE was radiation to bone (enzalutamide: N=181/278, 65.1% of patients with SREs; placebo: N=208/309, 67.3%) followed by spinal cord compression (enzalutamide: N=39/278, 14.0%; placebo: N=40/309, 12.9%) and pathological fractures (enzalutamide: N=39/278, 14.0%; placebo: N=31/309, 10.0%)2.

Treatment with enzalutamide was associated with a statistically significant reduction in the risk of experiencing a first SRE (HR: 0.718 [95% CI: 0.610, 0.844], p<0.0001; Figure B7). After an estimated median follow-up of 20.8 months and 19.3 months for the enzalutamide and placebo groups, respectively, the median time to first SRE was approximately 31 months in both groups.

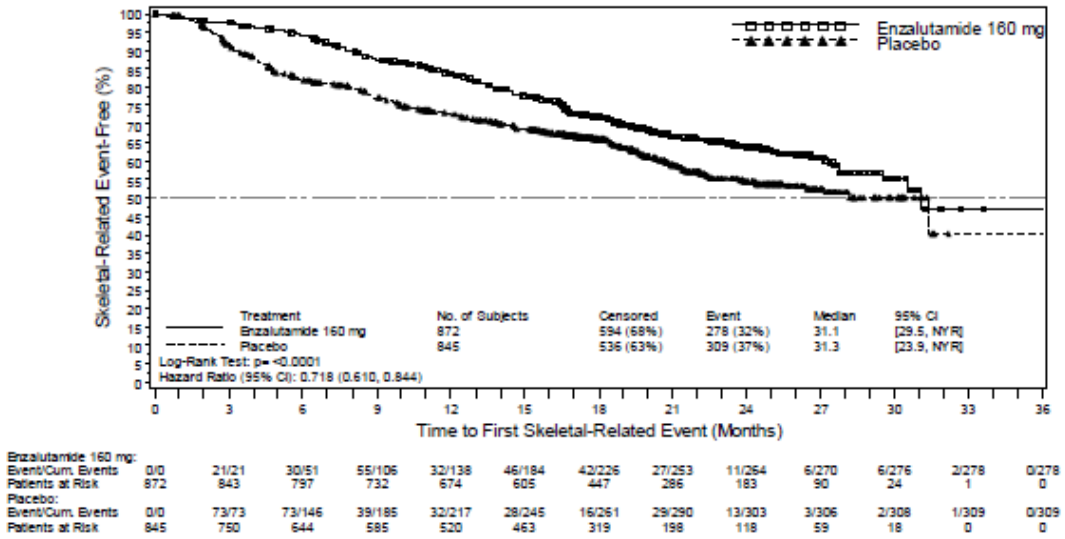
In a post-hoc analysis, the effect of enzalutamide on time to first SRE as measured by the hazard ratio was demonstrated to be consistently favourable across all subgroups pre-specified in the protocol.

Table B17 Incidence and time to first SRE (ITT)

	ENZA (N=872)	PLA (N=845)
Patients with SREs during the study, n (%)	278 (31.9%)	309 (36.6%)
Radiation to bone*	181 (65.1%)	208 (67.3%)
Surgery to bone*	11 (4.0%)	11 (3.6%)
Pathologic bone fracture*	39 (14.0%)	31 (10.0%)
Spinal cord compression*	39 (14.0%)	40 (12.9%)
Change of antineoplastic therapy to treat bone pain*	16 (5.8%)	29 (9.4%)
Censored observations	594 (68.1%)	536 (63.4%)
Time to first SRE (months)		
25% percentile	16.6	10.1
Median (95% CI)	31.1 (29.5, NYR)	31.3 (23.9, NYR)
75% percentile	NYR	NYR
Unstratified Analysis		
Hazard ratio (95% CI)	0.718 (0.610, 0.844)	
P-value (log-rank)	<0.0001	

Source: PREVAIL Clinical Study report2
Abbreviations: CI: confidence interval; ENZA: enzalutamide; ITT: intent-to-treat; NYR: not yet reached; PLA: placebo; SRE: skeletal-related event.
*These values have been calculated over the number of with one or more SRE during the study. When considering the overall ITT population, the proportion of patients with radiation to bone, surgery to bone, pathologic bone fracture, spinal cord compression and change of antineoplastic therapy to treat bone pain were 20.8%,1.3%, 4.5%, 4.5%; and 1.8%, respectively in the enzalutamide arm and 24.6%, 1.3%, 3.7%, 4.7%, and 3.4%, respectively in the placebo arm.

Figure B7 Time to first SRE (ITT)



Source: PREVAIL Clinical Study report2

Time to initiation of cytotoxic chemotherapy

A total of 308 patients (35.3%) in the enzalutamide group and 515 patients (60.9%) in the placebo group initiated treatment with a subsequent cytotoxic chemotherapy agent (Table B18, Figure B8). Treatment with enzalutamide was associated with a statistically significant delay in the time to initiation of cytotoxic chemotherapy. The median time to initiation of cytotoxic chemotherapy was 28.0 months in the enzalutamide group versus 10.8 months in the placebo group, with a median difference of 17.2 months (HR: 0.349, [0.303, 0.403], p<0.0001)2. Patients could have received therapies other than cytotoxic chemotherapy (e.g., non-cytotoxic therapy) between treatment discontinuation and initiation of cytotoxic chemotherapy. This accounts for the gap between median time to treatment discontinuation (17.71 months for enzalutamide and 4.55 months for placebo) and time to initiation of cytotoxic chemotherapy.

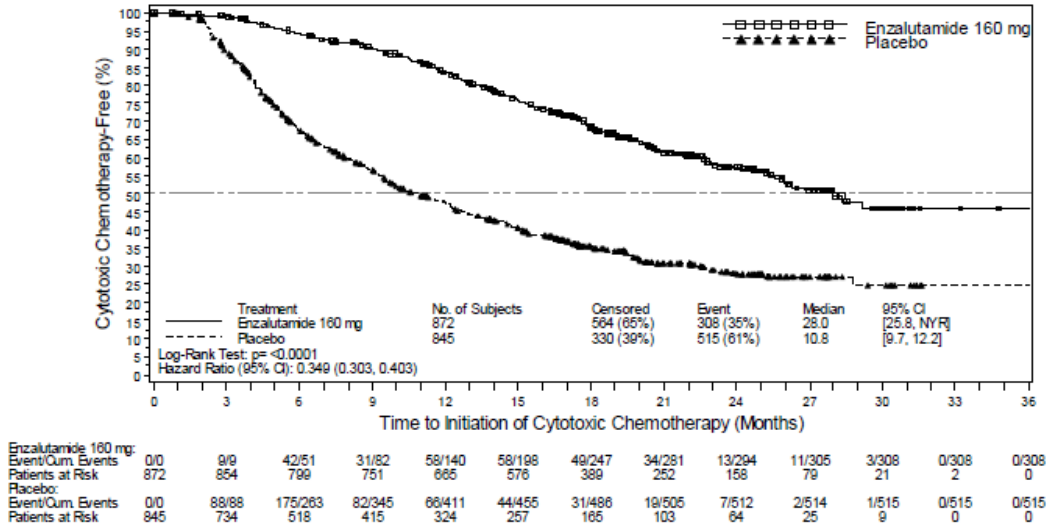
The most common initial cytotoxic chemotherapy was docetaxel which was administered to 90.5% (N=745/823) of patients who initiated cytotoxic chemotherapy.

Table B18 Time to initiation of cytotoxic chemotherapy

Time to Initiation of Cytotoxic Chemotherapy	ENZA (N=872)	PLA (N=845)
Initiation of cytotoxic chemotherapy status		
Events	308 (35.3%)	515 (60.9%)
Docetaxel first	276 (31.7%)	469 (55.5%)
Cabazitaxel first	15 (1.7%)	27 (3.2%)
Other chemo first	19 (2.2%)	21 (2.5%)
Censored[a]	564 (64.7%)	330 (39.1%)
Time to initiation of cytotoxic chemotherapy (months)[a,b]		
Censored	564 (64.7%)	330 (39.1%)
25th percentile	15.3	4.9
Median (95% CI)	28.0 (25.8, NYR)	10.8 (9.7, 12.2)
75th percentile	NYR	28.8
P-value (unstratified)	<0.0001	
Hazard ratio (95% CI)[c]	0.349 (0.303, 0.403)	
Median follow-up time based on reverse Kaplan-Meier estimates (months)	19.6	19.4

Source: PREVAIL Clinical Study report2
Abbreviations: ENZA: enzalutamide; ITT, intent-to-treat; NYR, not yet reached; PLA: placebo.
[a] Patients who did not start cytotoxic chemotherapy at the time of analysis data cut-off are censored at date of last assessment indicating no evidence of cytotoxic chemotherapy usage.
[b] Based on Kaplan-Meier estimates.
[c] Based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide.

Figure B8 Time to initiation of cytotoxic chemotherapy (ITT)



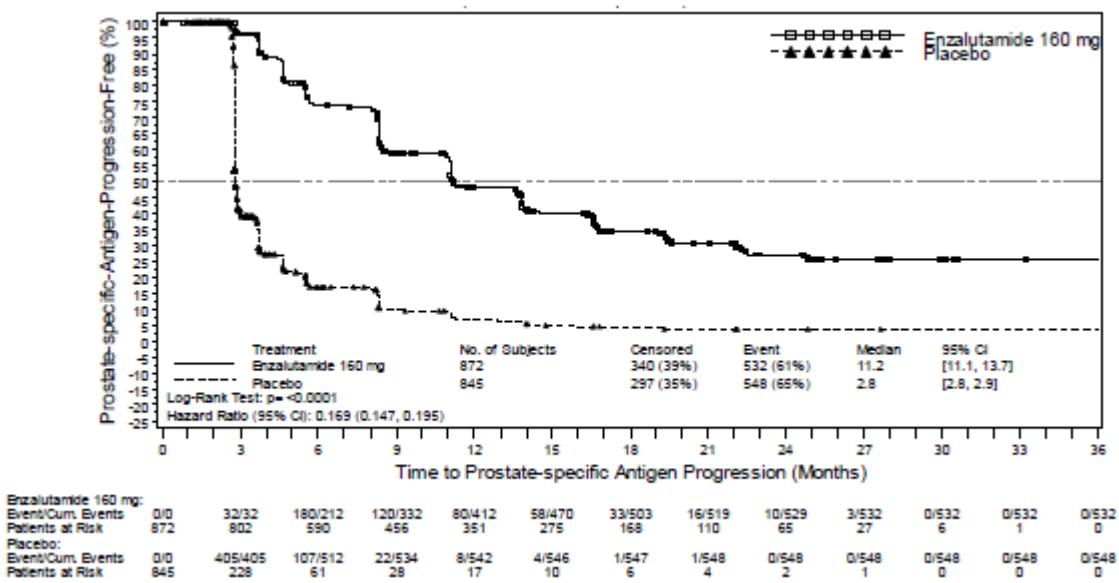
Source: PREVAIL Clinical Study report2
Hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring enzalutamide.

Time to PSA progression

In PREVAIL, 532 (61.0%) patients in the enzalutamide arm and 548 (64.9%) patients in the placebo arm experienced PSA progression during the study. Median time to PSA progression was significantly longer for enzalutamide (11.2 months, 95% CI [11.1; 13.7]) than with placebo (2.8 months, 95% CI [2.8; 2.9]) (Figure B9). Enzalutamide delayed time to PSA progression by 83.1% over placebo (HR: 0.169 [95% CI: 0.147, 0.195], p<0.0001)2.

Median follow-up based on reverse Kaplan-Meier estimation was [redacted] months for the enzalutamide group and [redacted] months for the placebo group.

Figure B9 Time to PSA progression (ITT)

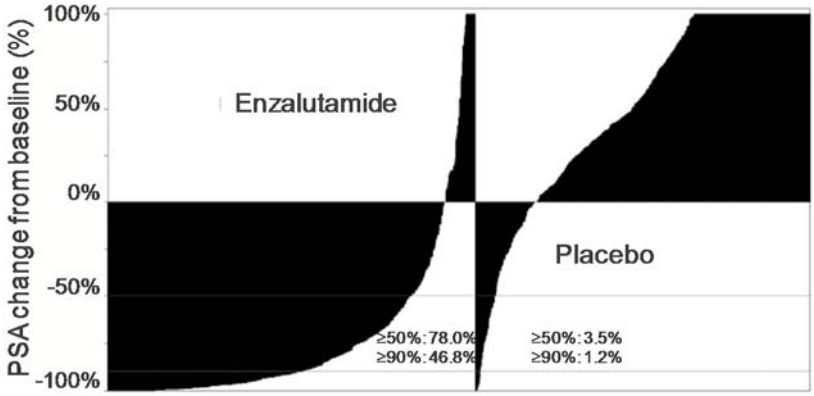


Source: PREVAIL Clinical Study report2

PSA response

When compared with placebo, enzalutamide led to a greater PSA response defined as ≥50% reduction in PSA from baseline to the lowest postbaseline PSA value (enzalutamide: N=666/854, 78.0%; placebo: N=27/777, 3.5%; p<0.0001)2. Similarly, the proportion of patients with a confirmed ≥90% PSA decrease was also significantly higher in the enzalutamide arm (N=400/854, 46.8%) than in the placebo arm (N=9/777, 1.2%; p<0.0001)2. The majority of patients treated with enzalutamide showed substantial decreases in PSA levels, as compared with a small minority of patients treated with placebo who had decreases in PSA levels (Figure B10).

Figure B10 Waterfall plot of PSA response



Source: PREVAIL Clinical Study report2
Abbreviations: ≥50%: ≥50% decline in PSA levels; ≥90%: ≥90% decline in PSA levels.
To simplify data presentation for this analysis, the maximal PSA increase was set at 100%, although PSA could be more than double.

Objective radiographic response

The objective response rate (ORR) defined as proportion of patients with complete or partial response as best tumour response was statistically significantly higher with enzalutamide (58.8%) than with placebo (5.0%, p<0.0001).

Similarly, enzalutamide was associated with more patients with stable disease and fewer patients with progressive disease (Table B19).

Table B19 Best overall radiographic response (ITT)

	ENZA (N=396)	PLA (N=381)
With at least 1 post-baseline assessment	382 (96.5%)	353 (92.7%)
With no post-base line assessment	14 (3.5%)	28 (7.3%)
Best overall response for the study		
Complete response	78 (19.7%)	4 (1.0%)
Partial response	155 (39.1%)	15 (3.9%)
Stable disease	128 (32.3%)	210 (55.1%)
Progressive disease	21 (5.3%)	124 (32.5%)
Inevaluable	14 (3.5%)	28 (7.3%)
Analysis		
Objective responses (complete and partial response)	233 (58.8%)	19 (5.0%)
Rate (95% CI)	53.8-63.7%	3.0-7.7%
Difference in objective response rate [95% CI] between the 2 groups	53.85% [48.53, 59.17%]	
P-value (Cochran-Mantel-Haenszel mean score test)	<0.0001	

Source: PREVAIL Clinical Study report2
Abbreviations: CI: confidence interval; ENZA: enzalutamide; PLA: placebo.
Only patients with measurable soft tissue disease (i.e., at least 1 target lesion identified per RECIST 1.1) at screening are included in this analysis. All percentages are based on number of patients with measurable soft tissue disease at screening in each treatment group.
[a] Response categories are based on target, nontarget, and new lesions. No confirmation is required. Patients with no post-baseline assessment are included in the category of nonevaluable.
[b] The best overall soft tissue objective response is defined as PR or CR based on investigator assessments of target, nontarget, and new lesions while on study treatment.
[c] Enzalutamide minus placebo, based on exact binomial 95% CI (Clopper-Pearson).
[d] Based on standard normal approximation.
[e] Based on unstratified Cochran-Mantel-Haenszel score test.

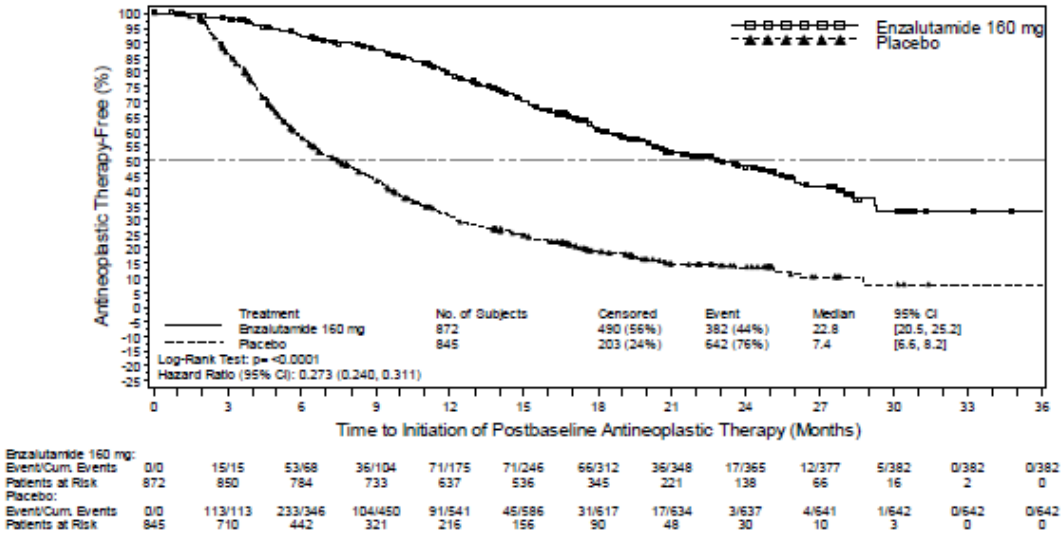
A post-hoc analysis was performed comparing best objective response rate in the subset of patients with measurable visceral disease at screening, which included 71 patients (8.1%) in the enzalutamide group and 80 patients (9.5%) in the placebo group. The results for this subset (i.e., patients with visceral disease) were comparable to those for the total study population. The proportion of patients with a complete and a partial response was 8.5% (N=6) and 43.7% (N=31) respectively in the enzalutamide group vs 0% and 1.3% (N=1) respectively in the placebo group. The objective response rate was 52.1% (N=37) and 1.3% (N=1) in the enzalutamide and placebo groups, respectively.

Time to first post-baseline antineoplastic therapy

In addition to time to first post-baseline cytotoxic chemotherapy (secondary endpoint), time to first post-baseline antineoplastic therapy was also assessed where antineoplastic therapy was defined as cytotoxic, hormonal, or investigational therapy.

A total of 382 patients (43.8%) in the enzalutamide group and 642 patients (76.0%) in the placebo group initiated treatment with a post-baseline antineoplastic therapy. Treatment with enzalutamide was associated with a statistically significant delay in the time to first post-baseline antineoplastic therapy. The median time to first post-baseline antineoplastic therapy was 22.8 months in the enzalutamide group versus 7.4 months in the placebo group, a median difference of 15.4 months (HR: 0.273, 95% CI: [0.240, 0.311], p < 0.0001)(Figure B11). Median follow-up times based on reverse Kaplan-Meier estimation were 19.8 months for the enzalutamide group and 19.4 months for the placebo group (Table B14).

Figure B11 Time to first post-baseline antineoplastic therapy (ITT)



Source: PREVAIL Clinical Study report

FACT-P response and other FACT-P related outcomes

FACT-P was administered at baseline, at Weeks 5 and 13 and every 12 weeks thereafter until disease progression. Completion rates for FACT-P declined over time in both treatment groups due to study drop-out. The dropout rate was much higher in the placebo arm mostly due to a higher rate of progressive disease. In contrast, completion rates for patients remaining in the study at each assessment time point (adjusted rates) were high in both arms and ranged between 91.5% and 100% for measurements conducted up to Week 133 (2.5 years)[53].

FACT-P response and FACT-P deterioration

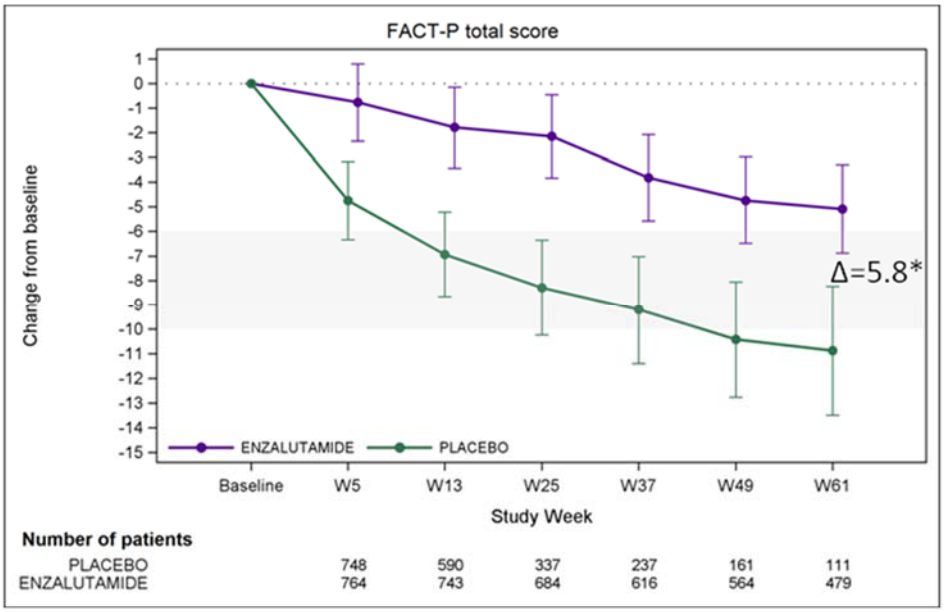
Enzalutamide was associated with a significantly higher proportion of patients with a positive QoL response as assessed by FACT-P than placebo, irrespective of whether the response was confirmed at 2 consecutive assessments (enzalutamide: 20.6%;

placebo: 8.9%; p<0.001) or not (enzalutamide: 39.6%; placebo: 22.9%; p<0.001)[53]. However, the proportion of patients with QoL deterioration at some stage during the study was also higher in the enzalutamide arm. While it did not reach statistical significance for the unconfirmed deterioration (enzalutamide: 54.6%; placebo: 51.6%; p=0.234), a significantly higher proportion of patients in the enzalutamide group had confirmed QoL deterioration (enzalutamide: 25.3%; placebo: 15.8%; p<0.001)[53]. A higher proportion of patients with QoL deterioration in the enzalutamide arm is likely to be due to QoL being collected for a longer period of time than for placebo.

Changes from baseline in FACT-P global score and domains

Patients in both treatment groups experienced reductions in their FACT-P scores, but clinically meaningful deterioration (>6 points[67]) was only observed in the placebo group (as early as Week 13 [Figure B12]). The treatment effect on the FACT-P total score was statistically significant and favoured enzalutamide at Week 61 (LS Mean: 5.8±1.3, p<0.001). The results of the mixed models with repeated measures (MMRM) analysis were confirmed by the pattern-mixture model results[53].

Figure B12 Adjusted mean change from baseline in FACT-P total score (ITT)

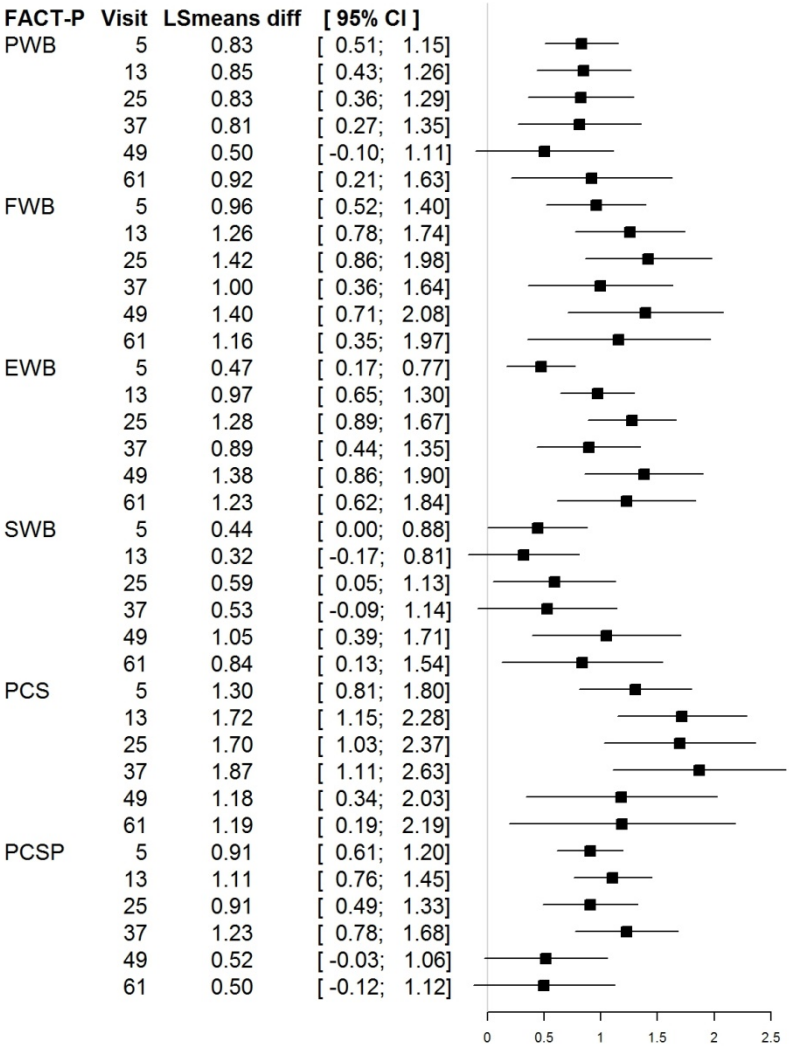


*p<0.05
Source: PREVAIL PRO Report[53]

Changes from baseline in FACT-P sub-domains

Differences between arms were assessed with a MMRM. Enzalutamide was associated with significantly improved QoL than placebo in all sub-domains at all time points except for physical well-being at Week 49, social well-being at Weeks 13 and 37, and prostate cancer subscale pain related score at Weeks 49 and 61 (Figure B13).

Figure B13 FACT-P total score and domain scores: LS means difference between changes from baseline with enzalutamide and with placebo (ITT)



Source: PREVAIL PRO report[53]
Abbreviation: EWB: emotional wellbeing; FACT-G: Functional Assessment of Cancer Therapy – General; FACT-P: Functional Assessment of Cancer Therapy – Prostate; FWB: functional wellbeing; PCS: prostate cancer scale; PWB: physical wellbeing; SWB: social wellbeing.

Time to QoL deterioration

Time to first QoL deterioration was assessed where deterioration was defined as a decrease in the score equal or higher than the minimal clinically important difference.

Enzalutamide significantly delayed time to first deterioration of QoL by 5.3 months compared with placebo (11.3 months, 95% CI: [11.1; 13.9] vs 5.6 months, 95% CI [5.5; 5.6]; log-rank test p-value <0.001). The HR was 0.625 (95% CI: [95% CI: 0.542; 0.720]; p<0.001)[53].

Pain-related outcomes

Several pain-related endpoints were assessed as exploratory endpoints using the BPI short form. The proportion of patients completing the BPI declined in both groups over time, primarily due to study drop-out. At the last assessment (Week 25), completion rates were lower in the placebo group (N=364/845; 43.1%) than in the enzalutamide group (N=719/872; 82.5%). When adjusted for study attrition, completion rates exceeded 90.0% in both treatment groups at all time-points[53].

Pain progression

Pain progression was assessed using the worst pain (item #3 of the BPI), the pain severity composite score and the pain interference composite score. Irrespective of the BPI score used, the proportion of patients with pain progression on BPI was significantly lower with enzalutamide than with placebo[53]:

- 41.0% (N=330/872) in the enzalutamide arms vs 50.5% (N=317/845) in the placebo arm for the pain severity composite score (p<0.001)
- 41.0% (N=330/872) in the enzalutamide arms vs 49.4% (N=312/845) in the placebo arm for the pain at its worst (item #3 of the BPI) (p=0.002)
- 31.3% (N=247/872) in the enzalutamide arms vs 41.6% (N=255/845) in the placebo arm for the pain interference composite score (p<0.001).

However, when consideration was limited to patients with confirmed progression, no significant differences were observed between treatment arms.

Time to pain progression

Time to pain progression was assessed using the worst pain severity, the average pain severity and the pain interference scores.

Median time to worst pain severity was 5.65 months (95% CI [5.62; 5.72]) and 5.55 months (95% CI [5.36; 5.55]) in the enzalutamide and placebo arms, respectively. Enzalutamide significantly reduced (by 38%) the risk of worst pain severity compared to placebo (HR=0.62, 95%CI: [0.53; 0.74]; p<0.001)[53].

Median time to average pain progression was 5.65 months (95% CI [5.59; 5.68]) and 5.55 months (95% CI [3.09; 5.55]) in the enzalutamide and placebo arms, respectively. Enzalutamide was associated with a 40% reduction in the risk of average pain severity compared to placebo (HR=0.60, 95%CI: [0.51;0.71]; p<0.001)[53].

Enzalutamide was associated with a 43% reduction in the risk of pain interference progression compared to placebo (HR=0.57, 95%CI: [0.48; 0.69]; p<0.001)[53]. Median time to pain interference progression was 5.82 months (95% CI [5.72; not reached yet]) with enzalutamide and 5.62 months (95% CI [5.55; 5.68]) with placebo.

Changes in pain severity and pain interference

Changes in pain severity were assessed with the BPI-SF. The severity of pain increased in both treatment arms however, the increase between baseline and Week 25 was significantly greater in the placebo arm (mean change: +0.79, 95% CI [(0.587, 1.000]) than with enzalutamide (mean change: +0.52, 95% CI [0.336, 0.697]; Table B20)[53].

Similarly, a significant increase in the level of pain interference with daily activities was observed in both treatment arms, but the increase at Weeks 23 and 25 were significantly higher with placebo than enzalutamide (p<0.001).

Table B20 Changes in pain severity and pain interference between baseline and Week 25

	Adjusted LS mean (SE)			
	ENZA	**PLA**	**Treatment difference**	**P-value**
Change in pain severity	0.52 (0.09)	0.79 (0.11)	-0.28 (0.09)	0.002
Change in pain interference	0.58 (0.11)	0.99 (0.12)	-0.41 (0.11)	<.001

Source: PREVAIL PRO report[53]
Abbreviations: ENZA: enzalutamide; PLA: placebo.

EQ-5D

In the original statistical analysis plan, no statistical tests were programmed regarding any difference in QoL as measured by the EQ-5D between treatment groups or over time. In addition, the initial analysis (presented in the Clinical Study Report2) covered only the first 25 weeks of the study. A post-hoc analysis has been conducted where change from baseline, and time to QoL deterioration were also analysed[53].

The unadjusted and adjusted (for study attrition) completion rates are provided in Table B21. The unadjusted completion rates declined in both groups over time, primarily due to study drop-out. This decline is more marked in the placebo group than in the enzalutamide group. At Week 61, 60.2% (N=525/872) of enzalutamide patients have responded to the EQ-5D instrument, while 13.8% (N=117/845) of placebo patients have data. From Week 61 onwards, the rates of completion were too low (particularly in the placebo arm) to draw any conclusions.

Overall, 98.2% (N=856) and 97.6% (N=825) of patients in the enzalutamide and placebo arms respectively had at least one baseline value; 93.8% (N=818) and 74.6% (N=630), respectively had baseline and at least one post-baseline values[53].

Table B21 Proportion of patients with EQ-5D post-baseline data

EQ-5D	Completion rates		Eligible pts		Adjusted completion rates	
	ENZA N (%)	PLA N (%)	ENZA	PLA	ENZA N (%)	PLA N (%)
Baseline	856 (98.2%)	825 (97.6%)	872	845	856 (98.2%)	825 (97.6%)
Week 13	810 (92.9%)	629 (74.4%)	835	653	810 (97.0%)	629 (96.3%)
Week 25	747 (85.7%)	367 (43.4%)	777	387	747 (96.1%)	367 (94.8%)
Week 37	672 (77.1%)	267 (31.6%)	716	280	672 (93.9%)	267 (95.4%)
Week 49	611 (70.1%)	176 (20.8%)	643	185	611 (95.0%)	176 (95.1%)
Week 61	525 (60.2%)	117 (13.8%)	554	129	525 (94.8%)	117 (90.7%)
Week 73	426 (48.9%)	79 (9.3%)	457	87	426 (93.2%)	79 (90.8%)
Week 85	268 (30.7%)	43 (5.1%)	288	48	268 (93.1%)	43 (89.6%)
Week 97	181 (20.8%)	27 (3.2%)	192	28	181 (94.3%)	27 (96.4%)
Week 109	119 (13.6%)	20 (2.4%)	125	20	119 (95.2%)	20 (100.0%)
Week 121	59 (6.8%)	5 (0.6%)	62	5	59 (95.2%)	5 (100.0%)
Week 133	13 (1.5%)	2 (0.2%)	13	2	13 (100.0%)	2 (100.0%)
Week 145	1 (0.1%)	0 (0.0%)	2	0	1 (50.0%)	0 (0.0%)

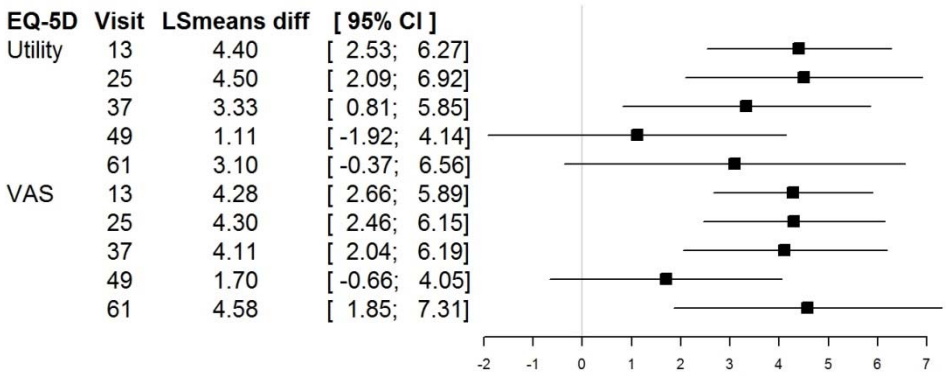
Source: PREVAIL PRO report[53]
Abbreviations: CI: confidence interval; ENZA: enzalutamide; EQ-5D: European Quality of Life Five-Domain Scale; ITT: intent-to-treat; PLA: placebo.

At baseline, the majority of patients in both arms scored level 1 for the Mobility, Self-Care, Usual Activities and Anxiety/Depression domains, while the proportion of patients who scored level 1 for Pain/Discomfort was comparable to those with level 2. Only 0.0%-0.5% of patients in the placebo arm and 0.0%-0.8% of patients in the enzalutamide arm scored level 3 for any of the domains. The baseline mean health state was slightly higher for enzalutamide (77.2±16.7) than for placebo (75.9±17.5)[53].

A MMRM was used to compare differences between treatment arms (Figure B14). The treatment effect on the time-to-trade-off derived EQ-5D utility index weights favoured enzalutamide at Week 61 (LS Mean: 0.03±0.02), but did not reach statistical significance (p=0.080). By contrast, a significant lower decrease between baseline and Week 61 in the VAS score was observed for patients treated with enzalutamide than with placebo (LS Mean: 4.58±1.39; p=0.001).

The treatment effect of enzalutamide over the whole study was also analysed using the MMRM and showed a utility gain of 0.02.

Figure B14 Treatment differences for EQ-5D instrument - MMRM analysis



Source: PREVAIL PRO report[53]
Due to the reduction in the effective sample size, only data up to week 61 were considered in the analysis. Values for utility index are multiplied by 100 to make the scale comparable. MMRM=Mixed model repeated measures.

The treatment benefit of enzalutamide observed with the MMRM analysis was confirmed by the pattern-mixture model results with which, the differences between arms was statistically significant at all time points up to Week 61, inclusive[53].

Time to HRQL deterioration as assessed with EQ-5D was also assessed. Enzalutamide was associated with significantly longer time to deterioration in EQ-5D utility index score (19.19 months vs 11.07 months for placebo; log-rank test p-value <0.001) and EQ-5D VAS score (22.14 months vs 13.83 months; log-rank test p-value <0.001). The HR was 0.62 (95%CI: [0.52; 0.73]; p<0.001) for the EQ-5D utility index score and 0.67 (95%CI: [0.56; 0.80]; p<0.001) for the VAS score[53].

6.5.3.4 Additional information

Time to treatment discontinuation (TTD) and OS adjustment for any post-study treatment given 2nd line that differed from clinical practice were calculated for modelling purposes. The results of these two analyses are presented here.

Time to treatment discontinuation

Physicians consider TTD as the most appropriate endpoint to assess for disease progression9.

Median TTD at the September cut-off was 17.71 (95% CI [16.59; 19.38]) and 4.55 (95% CI [4.11; 5.13]) months for the enzalutamide and placebo groups, respectively (Figure B15). These median times are comparable to median rPFS as assessed at the September data cut off-date (19.7 months; 95% CI: [18.1; 22.3] for enzalutamide and 5.4 months; 95% CI: [4.2; 5.6] for placebo).

The number of patients censored for this analysis was 367 in the enzalutamide group and 61 in the placebo group.

Figure B15 [redacted]

[redacted]

Source: Extrapolation report[81]

OS adjustment

The proportion of patients who switched (i.e., received post-study treatment 2nd line that differed from the treatment these patients would have received in current clinical practice) is provided in Table B22 for both data cut-offs. The post-study treatment patients received in PREVAIL are listed in Table B23.

Table B22 Proportion of switchers in PREVAIL

Data cut-offs	Enzalutamide (N=872)	Placebo (N=845)	All (N=1,717)
16 September 2013	[redacted]	[redacted]	[redacted]
30 June 2014	[redacted]	[redacted]	[redacted]

Source: OS adjustment report[37]

Table B23 Post-study treatment received 2nd line in PREVAIL

	September 2013 cut-off		June 2014 cut-off	
	Placebo (N=845)	**Enzalutamide (N=872)**	**Placebo (N=845)**	**Enzalutamide (N=872)**
Docetaxel	401 (47.5%)	228 (26.1%)	[redacted]	[redacted]
Hormonal treatments	16 (1.9%)	11 (1.3%)	[redacted]	[redacted]
Lutamide	45 (5.3%)	14 (1.6%)	[redacted]	[redacted]
Enzalutamide	**0 (0.0%)**	**1 (0.1%)**	[redacted]	[redacted]
Abiraterone	**90 (10.7%)**	**61 (7.0%)**	[redacted]	[redacted]
Cabazitaxel	**22 (2.6%)**	**14 (1.6%)**	[redacted]	[redacted]
Sipuleucel -T	**9 (1.1%)**	**10 (1.1%)**	[redacted]	[redacted]
Investigational	**43 (5.1%)**	**28 (3.2%)**	[redacted]	[redacted]
Other chemotherapy for prostate cancer cytotoxic	**14 (1.7%)**	**14 (1.6%)**	[redacted]	[redacted]
Other chemotherapy for prostate cancer non-cytotoxic	**2 (0.2%)**	**1 (0.1%)**	[redacted]	[redacted]

In bold, treatments for which OS was adjusted for

Adjustment of OS data was conducted using two different methods: the two stage and the IPCW methods. Similar results were obtained with both methods and suggested a higher treatment effect compared to the unadjusted ITT analysis[37]. The results of both methods for both data cut-offs are presented in Table B24. It is important to note that in contrast to HRs obtained from the unadjusted and two-stage analyses, the HR obtained from the IPCW method is adjusted for baseline covariates.

Table B24 Adjusted OS with the IPCW and two-stage methods

	HR [95% CI]	
	September 2013	**June 2014**
Unadjusted OS	0.706 [0.595;0.837]	[redacted]
Adjusted OS		
IPCW	[redacted]	[redacted]
Two stage method	[redacted]	[redacted]

Source: OS adjustment report[37]

Both methods are associated with theoretical and practical limitations[37]. The IPCW method is a well-known method developed in the causal inference field of statistics and holds a strong theoretical background. On the other hand, the two-stage method was proposed as a simple alternative to the two-stage structural nested model that could adjust estimates of the treatment effect on OS in the presence of switching. The method partially controls for time-dependent confounders in a simple manner, by making use of a secondary “baseline” after which treatment switching is permitted to occur[71]. It could be argued that the IPCW method is stronger at a theoretical level. However, in this case the advantages of the IPCW are reduced because no covariate data are available beyond treatment discontinuation.

In addition, it is important to note that recensoring is advised for the two-stage method. In the PREVAIL study we considered that recensoring was prone to bias, because:

- There is high degree of recensoring both in number of events lost and visual inspection of the KM curves of the adjusted datasets
- The adjusted treatment effect estimate with and without recensoring is not significantly different
- KM curves when applying recensoring suggest the curves converge, while longer term observed OS data maintain a gap between them, despite treatment switching.

Hence we concluded that in this case the bias associated with not recensoring may be less than the bias associated with recensoring, due to the loss of longer-term information. A limitation for both methods is that they rely on the no unmeasured confounders assumption. This assumption cannot be tested, and in practice this is unlikely to be perfectly true, but the methods are likely to work adequately if the assumption is approximately true; that is, there are no important independent predictors missing[71]. A thorough list of covariates was compiled after assessment of the collected data in the trial combined with consultation with clinical experts. We believe therefore that the "no unmeasured confounders" assumption is approximately true and reasonable in the PREVAIL study case, although not perfect, because a lot of data on lots of covariates were collected, but in some cases data collection did not continue beyond study drug discontinuation, which would have been preferable.

A potential issue in both methods, given that in this case no covariate data were collected after treatment discontinuation, is that time-dependent confounding could occur between the time of treatment discontinuation and the time of treatment switch. However, the gap between treatment discontinuation and the time of treatment switch observed in the PREVAIL study was not substantial and was similar between the two arms with an average duration of 2-2.5 months. This gap is likely due to hospital or clinic-related logistical reasons which delay initiation of new antineoplastic treatment. Still, the IPCW method has the advantage over the two-stage method because it includes time since treatment discontinuation in the estimation process.

Based on the limitations of both methods, the IPCW was deemed the most appropriate adjustment method for PREVAIL and was therefore used in the base case of the economic evaluation. The IPCW method was chosen for the economic base case based on its stronger theoretical background, and clinical plausibility of assumptions. However, the two-stage method is used in a scenario analysis.

6.5.3.5 Conclusions

- PREVAIL was a randomised double-blind placebo-controlled study comparing enzalutamide to placebo in adults with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated.

- All primary and secondary endpoints were met.

- PREVAIL showed that enzalutamide leads to significantly longer OS than placebo in chemo-naïve patients with asymptomatic or mildly symptomatic

mHRPC despite a higher proportion of patients in the placebo arm being switched to therapies some of which with the potential to prolong survival, after discontinuation of the trial medication.

- PREVAIL also showed that enzalutamide leads to significantly longer rPFS than placebo in chemo-naïve patients with asymptomatic or mildly symptomatic mHRPC.

- Superior treatment effect of enzalutamide over placebo was also observed in the radiographic tumour response, PSA response, pain palliation and HRQL. In terms of HRQL, enzalutamide led to a significantly lower decrease in the FACT-P HRQL total score and all domains except for prostate cancer subscale pain related score than placebo at Week 61. Differences in favour of enzalutamide were also observed for the EQ-5D utility index and the BPI pain scores (Pain severity and Pain Interference).

- The favourable HRQL observed in patients treated with enzalutamide resulted in a gain of +0.02 utilities when compared with placebo.

- The favourable effect of enzalutamide over placebo on OS and rPFS was observed in all the patient subgroups pre-specified in the study protocol.

- Overall, the benefits of enzalutamide in asymptomatic or mildly symptomatic mHRPC patients in whom immediate chemotherapy is not yet clinically indicated appear clear, are robust and of clinical relevance.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT

results are heterogeneous, try to provide an explanation for the heterogeneity.

- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No meta-analysis could be performed because only one RCT that compared enzalutamide with placebo in the treatment of asymptomatic or mildly asymptomatic patients with mHRPC was identified by the systematic literature review (see sections 6.1 and 6.2).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/A.

6.7 *Indirect and mixed treatment comparisons*

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Relevant studies to be included in the ITC were identified using the strategy described in sections 6.1 and 6.2. No additional searches to those detailed in these two sections and Appendix 2 were conducted for the ITC. Following identification of relevant studies, the next stage in the ITC was to assess the similarity of the trials and to determine whether it would be appropriate to combine the trials in an ITC.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Details of the inclusion and exclusion criteria employed for the SLR and ITC are presented in Table B2.

Following assessment and exclusion of studies based on title, abstract and full text, 38 clinical study-related references representing 2 RCTs in the chemo-naïve setting were identified[46].

Both RCTs were deemed relevant for inclusion in an ITC (PREVAIL and COU-AA-302[82,83]). However an ITC between enzalutamide and abiraterone is only possible using the control arm of each RCT as the common arm. The included RCTs share a similar design and population however, the markedly different proportion of patients

on corticosteroids in the control arm of each study is likely to severely bias the outcomes of the ITC.

Therefore, based on the advice of clinical and economic experts, a naïve comparison between enzalutamide and abiraterone was applied to the base case economic model used in this submission. Nevertheless, an ITC using the control arm of each study as the common arm was also conducted and used in one of the scenario analyses of the economic model.

The similarities and differences are discussed below.

Table B25 List of studies identified in the SLR relevant to the decision problem

Study acronym	Population	Intervention	Comparator	Key references
PREVAIL	Adult men with mHRPC who are asymptomatic or mildly symptomatic in whom chemotherapy is not yet clinically indicated	Enzalutamide 160 mg OD	Placebo	PREVAIL CSRBeer et al3
COU-AA-302*	Adult men with mHRPC who are asymptomatic or mildly symptomatic in whom chemotherapy is not yet clinically indicated	Abiraterone 1,000 mg once daily plus prednisone 10 mg OD	Prednisone 10 mg OD plus placebo	Ryan et al[83] Rathkopf et al[82] Ryan et al8

Abbreviations: CSR: clinical study report; mHRPC: metastatic hormone-relapsed prostate cancer; OD: once daily.
*As already mentioned, the outcomes of the final analysis of COU-AA-302 study were published by Ryan et al7 in the Lancet Oncol shortly before this submission. This article has not been included in this submission. All reference to final results relate to those presented at ESMO 2014[8].

Consideration of identified studies for inclusion in the indirect comparison

Two studies were identified that would allow an ITC of enzalutamide vs abiraterone from a methodological point of view: PREVAIL and COU-AA-302. To be able to perform the ITC the comparator arm in each study were considered similar. However, the treatment received in the comparator arms differed in the:

- proportion of patients exposed to prednisone: 100% in the placebo arm of COU-AA-302 vs 30.2% in the placebo arm of PREVAIL
- reason for the need of corticosteroids: to avoid toxicity in COU-AA-302 and supportive treatment in PREVAIL.

For the ITC, the placebo arm in COU-AA-302 (100% of patients on prednisone) was assumed to have the same treatment effect as the placebo arm in PREVAIL. The

prednisone arm in COU-AA-302 was assumed to have the same impact on OS and any other endpoint as the placebo arm in PREVAIL.

It is unclear whether corticosteroids have any effect on the efficacy of abiraterone. The effect of corticosteroids is multimodal. Corticosteroids inhibit prostate cancer growth through pleiotropic effects on suppression of adrenocorticotropic hormone (ACTH) secretion and downstream adrenal androgen production as well as effects on cytokines and transcription factors. Thus, the incremental benefit of corticosteroids when given with abiraterone (which itself effectively suppresses adrenal androgen production) is not known. However, there is evidence that when given alone corticosteroids may have an impact on certain endpoints such as disease progression or burden of symptoms[5,6]. An effect on OS cannot be discarded either. Thus, exposure to corticosteroids for all patients in the control arm of COU-AA-302 study may underestimate the treatment benefit of abiraterone over placebo. Using the control arm as the common arm in the ITC may also benefit enzalutamide over abiraterone. A possibility to overcome this limitation would be to adjust the ITC for the possible treatment effect of corticosteroids when given alone. However, current evidence does not allow quantification of the effect of corticosteroids in chemo-naïve mHRPC patients and adjustment of the ITC.

Given the uncertainty of a possible treatment effect of the placebo arm in COU-AA-302, a naïve treatment comparison of the enzalutamide arm in PREVAIL and the abiraterone arm of COU-AA-302 has been conducted for the base case in the economic model. However, a naïve comparison is not devoid of limitations. COU-AA-302 was initiated 18 months prior to PREVAIL and the last patient was randomised more than 2 years before the last patient was randomised in PREVAIL. The different timing between studies has had an impact on the post-study treatment received by patients. A larger number of therapeutic options were available for PREVAIL patients after study treatment discontinuation than in the 3rd interim analysis of COU-AA-302 (used to inform the naive comparison). This limitation has been mitigated somewhat by conducting an OS adjustment in PREVAIL for 2nd line post-study treatment that differs from treatment given in clinical practice. An attempt was made to adjust for subsequent treatments in the abiraterone's manufacturer's submission, but the rationale and methodology were unclear, and had minimal effect on the hazard ratio. Moreover, whilst the baseline characteristics of patients enrolled in PREVAIL and COU-AA-302 are predominantly similar, there exist important differences. In particular, the enrolment in PREVAIL of patients with visceral disease. Consequently, a naive comparison is likely to be biased against enzalutamide.

Study methodology

A summary of the methodology of the two studies (PREVAIL and COU-AA-302) included in the ITC is provided in Table B26. The study design of PREVAIL and COU-AA-302 was comparable; both studies were randomised, double-blinded, placebo-controlled phase III trials. In addition, both studies had co-primary endpoints which were OS and rPFS.

Table B26 Comparative summary of methodology of RCTs included in the indirect comparison

	PREVAIL	COU-AA-302
Location	207 sites in 22 countries in North America, Europe,	151 sites worldwide in Australia, Belgium, Canada,

	PREVAIL	COU-AA-302
	Australia, and Asia. Overall, 153 patients from the UK participated	France, Germany, Greece, Italy, Netherlands, Spain, Sweden, the UK, and the US (12 study sites and 9.0% of patients were from the UK)
Design	Phase III, multinational, randomised, DB, PLA-controlled study	Phase III, multinational, randomised, DB, PLA-controlled study
Duration of study	The first patient was enrolled on 28 September 2010 and the last patient on 07 September 2012. Follow-up is ongoing	The first patient was enrolled on 28 April 2009 and the last patient on 23 June 2010. Follow-up is ongoing
Method of randomisation	Eligible subjects were randomised (1:1) using a centralised Interactive Web Response System (IWRS) and were stratified by study site.	Eligible subjects were randomised (1:1) using a centralised IWRS and were stratified by ECOG PS (0 vs 1)
Method of blinding (care provider, patient and outcome assessor)	Double blind: Patients and Investigators were blinded to the study drug. Placebo matched the enzalutamide tablets in size, colour and shape.	Double blind: Patients and Investigators were blinded to the study drug. Placebo matched the abiraterone acetate tablets in size, colour and shape. All subjects, family members, study personnel, and members of the Independent Data Monitoring Committee (IDMC) were to remain blinded to treatment assignment until completion of the study.
Intervention(s) (n =) and comparator(s) (n =)	ENZA: N=872 PLA: N=845	ABI+PRED: N=546 PLA+PRED: N=542
Primary outcomes	Two co-primary outcomes were OS and rPFS	Two co-primary outcomes were OS and rPFS
Secondary outcomes	• Time to first SRE • Time to initiation of cytotoxic chemotherapy • Time to PSA progression • PSA response (50% decrease) • Best overall soft tissue response on the basis of RECIST 1.1 • Safety	• Time to first opiate use for cancer pain • Time to initiation of cytotoxic chemotherapy for prostate cancer • Time to first established clinical deterioration in terms of ECOG PS by ≥1 grade • Time to first established PSA progression
Exploratory outcomes	• FACT-P response • Time to degradation of the FACT-P • EQ-5D • BPI	• PSA response rate • Objective response rate • Duration of response • Time to first

	PREVAIL	COU-AA-302
	• Time to first post-baseline antineoplastic therapy • PSA response ≥90%.	established analgesic progression • Functional status • Time to first established functional status deterioration • Time to first established progression in average pain intensity (BPI-SF) • Time to first established progression in worst pain intensity (BPI-SF) • Time to first established progression in pain interference
Post hoc analysis	• Time to treatment discontinuation	• Association between OS and rPFS • Multivariate OS analysis to assess baseline prognostic factor imbalances
Duration of follow-up	At the pre-specified September 2013 cut-off: • ENZA: 22.2 months • PLA: 22.4 months	• Third analysis: 27.1 months[82] • Final analysis: 49.4 months8 In the model, the OS included for abiraterone corresponds to that of the third analysis given that the Kaplan-Meier plots for the final analysis have not yet been published
Publications	PREVAIL CSR Beer et al3	Ryan et al[83] Rathkopf et al[82] Ryan et al8

Abbreviations: ABI: abiraterone; DB: double-blind; ECOG: Eastern cooperative oncology group; ENZA : enzalutamide; FACT-P: functional assessment of cancer therapy-prostate; PLA: placebo; PFS: progression-free survival; PRED: prednisone; PSA: prostate specific antigen; HRQL: health related quality of life; RECIST: response evaluation criteria In solid tumours; SRE: skeletal related events; BPI-SF: brief pain inventory short form.

The outcomes considered in the ITC and the sources used are provided in Table B27.

Table B27 Endpoints assessed and data sources for the indirect treatment comparison

	References used for enzalutamide	References used for abiraterone
OS	OS adjustment report[37]	IA3: Rathkopf et al[82] Final analysis: Ryan et al[83]
rPFS	Enzalutamide CSR2	IA3: Rathkopf et al[82]
Time to chemotherapy initiation	Beer et al3	IA3: Rathkopf et al[82]

Response rate	Beer et al3	IA3: Rathkopf et al[82]
Time to PSA progression	Beer et al3	IA3: Rathkopf et al[82]

Abbreviations: OS: overall survival; PSA: progression free survival; rPFS: radiographic progression-free survival; HRQL: health related quality of life.

The key efficacy study endpoint definitions assessed in PREVAIL and COU-AA-302 are summarised in Table B28.

Table B28 Key efficacy endpoints assessed in PREVAIL and COU-AA-302

Endpoint	PREVAIL	COU-AA-302
Co-primary endpoint		
OS	Time from randomisation to death of any cause	Same as in PREVAIL
rPFS	Time from randomisation date to the first objective evidence of radiographic disease progression (based on central imaging review) or death due to any cause within 168 days after treatment discontinuation, whichever was first.	The time from randomisation to the first evidence of radiographic disease progression, progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST criteria or death from any cause, whichever was first
Secondary & exploratory		
Time to first SRE	Time from randomisation to the first documented SRE defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. An alteration of analgesic medication for bone pain was not considered a SRE.	Not reported
Time to initiation of cytotoxic chemotherapy	Time from randomisation to the date of initiation of cytotoxic chemotherapy	Same as in PREVAIL
Time to PSA progression	The time to PSA progression was defined according to the PCWG2 guidelines	Same as in PREVAIL
PSA response ≥50%	≥50% reduction in PSA from baseline to the lowest post-baseline PSA value and confirmed by a consecutive assessment at least 3 weeks later	Same as in PREVAIL
Best overall soft tissue response	Objective response (complete response [CR], partial response [PR], stable disease, or progressive disease [PD]) of baseline measurable disease (i.e., target) lesions was assessed by investigators using RECIST 1.1	Same as in PREVAIL
FACT-P	Changes in total FACT-P score and domain scores from baseline were used to assess quality of life over time	Same as in PREVAIL
Time to degradation of HRQL according to FACT-P	Time from randomisation to date of degradation of FACT-P. Degradation on the FACT-P was defined as at least a 10-point decrease from baseline in the total score.	Same as in PREVAIL
EQ-5D	Changes from baseline	Same as in PREVAIL
Brief pain inventory	Changes from baseline in several items	Same as in PREVAIL
Time to first post-baseline antineoplastic therapy	Time from randomisation to date of first use of antineoplastic therapy defined as cytotoxic chemotherapy, noncytotoxic chemotherapy, ADT, approved immunotherapy, oestrogen, abiraterone,	Not assessed

Endpoint	PREVAIL	COU-AA-302
	and investigational agents for prostate cancer. New use of bisphosphonate therapy, denosumab, hormonal therapies to treat hot flush/anorexia, or a change in GnRH analogue treatment were not included in this analysis. As the protocol allowed for concomitant use of additional hormonal treatments for prostate cancer after the occurrence of confirmed radiographic progression or a SRE, the first new postbaseline antineoplastic therapy could have been initiated before the discontinuation of study drug.	
PSA response ≥90%	≥90% reduction in PSA from baseline to the lowest post-baseline PSA value and confirmed by a consecutive assessment at least 3 weeks later	Not assessed
Safety	Based on AEs, ECG and other vital signs	Same as in PREVAIL

Source: Enzalutamide CSR2; Manufacturer NICE submission for abiraterone[35]
Abbreviations: OS: overall survival; rPFS: Radiographic Progression Free Survival; RECIST: response evaluation criteria in solid tumors; SRE: Skeletal-Related Event.

In both studies the active treatment (enzalutamide and abiraterone) was associated with significantly better efficacy than the control arm.

Study participants

The study population of the PREVAIL and COU-AA-302 studies were comparable (Table B29). Similar selection criteria were applied and both studies included asymptomatic or mildly symptomatic patients with mHRPC in whom chemotherapy is not yet clinically indicated.

Similar demographic and baseline characteristics were observed in both studies. Median age was 70-71 years of age in PREVAIL3 and 71-72 in COU-AA-302[83], with 35.5% and 32.2% of patients aged 75 or more, respectively. The patients in both studies had a comparable duration of disease (median time since diagnosis: 5.1 – 5.5 years). The proportion of patients with bone metastases was equally similar with 83.3% of patients in PREVAIL3 and 81.4% of patients in COU-AA-302[83]. Both studies comprised patients with ECOG 0-1 exclusively. However, the proportion of patients with ECOG 1 tended to be higher in PREVAIL (ECOG 0: 68.1%; ECOG 1: 31.9%)3 than in COU-AA-302 (ECOG 0: 75.7%; ECOG 1: 24.5%)[83].

The main differences between the two trials relate to the proportion of white patients and patients with visceral disease. While only 77.1% of patients in PREVAIL were White, this percentage was 94.9% in COU-AA-302. Regarding the proportion of patients with visceral disease, while presence of visceral metastasis was an exclusion criterion in COU-AA-302, patients with lung and/or liver metastases could be enrolled in PREVAIL. Overall, 11.9% of patients in PREVAIL3 had visceral disease vs none in COU-AA-302[83].

Table B29 Demographics and baseline characteristics of men in COU-AA-302 and PREVAIL

	COU-AA-302	PREVAIL

	ABI + PRED (N=546)	PLA + PRED (N=542)	ENZA (N=872)	PLA (N=844)
Age				
Median (range)	71 (44-95)	70 (44-90)	72 (43-93)	71 (42-93)
≥75 years	185 (34%)	165 (30%)	317 (29.2)	364 (34.6)
Ethnicity				
American Indian or Alaska Native	-	-	1 (0.1%)	0 (0.0%)
Asian	(0.7)	(1.7)	85 (9.7%)	82 (9.7%)
Black or African American	(2.8)	(2.4)	21 (2.4%)	13 (1.5%)
Native Hawaiian or other Pacific Islander	(0.0)	(0.4)	1 (0.1%)	1 (0.1%)
White	(95.4)	(94.4)	669 (76.7%)	655 (77.5%)
Other, multiple, unknown	(1.1)	(1.1)	95 (10.9%)	94 (11.1)
Time since diagnosis (years)*				
Median (range)	5.5 (<1-28)	5.1 (<1-28)	5.2 (<1; 27.2)	5.4 (<1; 23)
Extent of disease				
N	542	540		
Bone only	274 (51%)	267 (49%)	348 (39.9%)	335 (39.6%)
Soft tissue or node	267 (49%)	271 (50%)	Soft tissue: 124 (14.2%) Node: 437 (50.1%)	Soft tissue: 149 (17.6%) Node: 434 (51.4%)
Visceral (lung or liver)	0 (0%)	0 (0%)	98 (11.2%)	106 (12.5%)
ECOG performance status				
0	413 (75.6)	409 (75.5)	584 (67.0%)	585 (69.2%)
1	133 (24.4)	133 (24.5)	288 (33.0%)	260 (30.8%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PSA				
Number of patients	470	454		
Median, ng/mL	22.3	21.0	54.1	44.2
Gleason score at initial diagnosis	488	508	838	808
≤7	225 (46%)	254 (50%)	414 (49.4)	385 (47.6%)
≥8	263 (54%)	254 (50%)	424 (50.6%)	423 (52.4%)
Missing				
Previous cancer therapy	544	542	872	845
Surgery	256 (47%)	244 (45%)	453 (51.9%)	419 (49.6%)
Radiotherapy	283 (52%)	303 (56%)	392 (45.0%)	380 (45.0%)
Hormonal	544 (100%)	542 (100%)	865 (99.2%)	838 (99.2%)
Other	82 (15%)	63 (12%)		
Screening BPI-SF pain score (worst pain over last 24 hours)				
N	532	522	859	840
0–1	353 (66%)	336 (64%)	569 (66.2%)	567 (67.5%)
2–3	169 (32%)	170 (33%)	275 (32.0%)	262 (31.2%)
≥4	10 (2%)	16 (3%)	15 (1.7%)	11 (1.3%)
Baseline LDH (ng/mL)				
Number of patients	543	536	871	844
Median (range)	187 (60; 871)	184 (87; 781)	185 (52; 1861)	185 (67; 2321)

Source: Ryan at al[83], PREVAIL Clinical Study Report2
Abbreviations: ABI: abiraterone; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; PLA: placebo; PRED: prednisone; PSA: prostate-specific antigen; SD: standard deviation.

*Time since diagnosis for patients in the PREVAIL study has been recalculated; original data are provided in months (enzalutamide: 62.7 months; 95% CI [0.2; 326.6]; placebo: 64.6 months; 95% CI [0.1; 275.4]).

Quality assessment

The quality assessment's of both the PREVAIL and COU-AA-302 studies can be found in Appendix 3, section 10.3 and appendix 5, section 10.5, respectively.

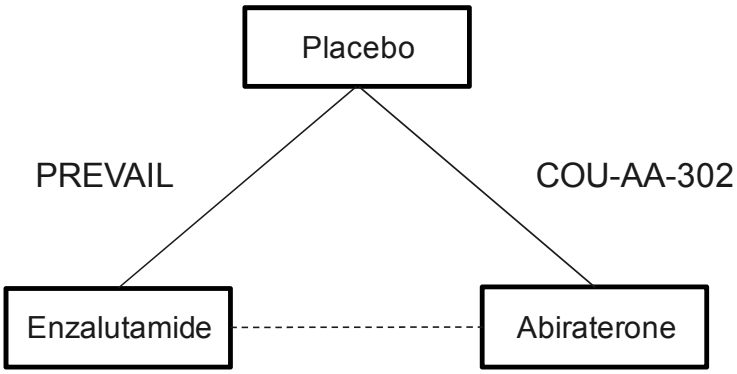
The methods used to generate random allocation sequence and for concealment of allocation sequence were reported for both studies and were judged as adequate. Blinding status was clear for both studies and neither of the studies showed any evidence of selective reporting. Overall, neither of the two studies used in the ITC were identified as being at a high risk of bias, resulting in the validity of the results not been affected.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

As indicated in section 6.7.2, the studies included in the ITC are PREVAIL and COU-AA-302. The ITC of enzalutamide with abiraterone was mediated via the placebo arm of each study.

The evidence network used for the ITC is depicted in Figure B16.

Figure B16 Evidence network used in the indirect treatment comparison



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

The outcomes considered in the ITC were OS, rPFS, time to cytotoxic chemotherapy initiation, and time to PSA progression. The data included for the indirect treatment comparison are presented in Table B30. In addition, complete or partial response as

best objective response as well as progressive disease as best objective response were included in the ITC (Table B31).

Table B30 Efficacy data included in the indirect treatment comparison for enzalutamide and abiraterone for time to endpoints

Outcome	HR [95% CI]	Data cut-off	Reference
ENZA vs PLA			
OS	[redacted]	June 2014 (unadjusted)	OS adjustment report[37]
	[redacted]	June 2014 (IPCW adjusted)	OS adjustment report[37]
rPFS	0.307 [0.267, 0.353]	September 2013 (investigator assessed)	PREVAIL CSR2
Time to chemotherapy initiation	0.349 [0.303, 0.403]	September 2013	Beer et al3
Time to PSA progression	0.169 [0.147, 0.195]	September 2013	Beer et al3
ABI vs PLA			
OS	0.79 [0.66; 0.95]	IA3 cut-off	Rathkopf 2014[82]
	0.80 [0.69; 0.93]	Final analysis	Ryan et al8
rPFS	0.52 [0.45, 0.61]	IA3 cut-off	Rathkopf 2014[82]
Time to chemotherapy initiation	0.62 [0.51, 0.72]	IA3 cut-off	Rathkopf 2014[82]
Time to PSA progression	0.50 [0.43, 0.58]	IA3 cut-off	Rathkopf 2014[82]

Abbreviations: ABI: abiraterone; ENZA: enzalutamide; HR: hazard ratio; IA3: third interim analysis; OR: odds ratio; OS: overall survival; PLA: placebo; rPFS: Radiographic Progression Free Survival.

Table B31 Efficacy data included in the indirect treatment comparison for enzalutamide and abiraterone for binomial endpoints

Outcome	n/N	Data cut-off	Reference
ENZA vs PLA			
Best overall response (CR+PR)	ENZA: 233/396 PLA: 19/381	September 2013	PREVAIL CSR2
Best overall response (PD)	ENZA: 21/396 PLA: 124/381	September 2013	PREVAILCSR2
ABI vs PLA			
Best overall response (CR+PR)	ABI+PRED: 79/220 PLA+PRED: 35/218	Third interim analysis	Ryan et al8
Best overall response (PD)	ABI+PRED: 4/220 PLA+PRED: 33/218	Third interim analysis	Ryan et al8

Abbreviations: ABI: abiraterone; CR: complete response; ENZA: enzalutamide; PD: progressive disease; PLA: placebo; PR: partial response; PRED: prednisone

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The outcomes were assessed on the log-hazard scale, therefore the data required for the ITC were log hazard ratios (logHR) and their standard errors (SEs). These data were available for the enzalutamide and abiraterone studies. The log(HR) and SE were approximated from the log scale CI after checking that the log scale CI was symmetric.

For the ITC enzalutamide vs abiraterone, it was assumed that the log HR follows a normal distribution. For each study it is necessary to define a baseline treatment b, to which all other treatments are compared. For ease of interpretation this will be usually be placebo (unless the study does not include placebo), however, the choice of baseline treatment will not affect the results.

- Define L_{jkb} as the observed log HR for treatment k relative to treatment b in trial j;
- Define σ_{jkb} as the standard error of the log HR for treatment k relative to treatment b in trial j.

For each treatment, other than the baseline treatment:

$$L_{jkb} \sim \text{Normal}\left(\theta_{kb}, \sigma_{jkb}^2\right) \qquad \text{[Equation 1]}$$

where:

$$\theta_{kb} = \delta_k - \delta_b \qquad \text{[Equation 2]}$$

The parameters δ_k and δ_b are the true log HRs for treatment k relative to placebo, and treatment b relative to placebo. The parameters δ_k and δ_b are given vague prior distributions: Normal $\left(0,100^2\right)$.

6.7.6 Please present the results of the analysis.

The results of the ITC for OS, rPFS, time to PSA progression and time to initiation of cytotoxic chemotherapy are provided in Table B32. The results for the best overall response are provided in Table B33. When compared with abiraterone, enzalutamide is associated with a significantly lower likelihood of radiographic disease progression (HR: [redacted] PSA progression (HR: [redacted] and initiation of cytotoxic chemotherapy (HR[redacted]). In terms of OS, different comparisons were carried out. For unadjusted OS, no significant differences were observed between enzalutamide and abiraterone. At the time of carrying out the ITC, no data were available for abiraterone OS adjusted for switching. When using IPCW adjusted OS for enzalutamide and non-adjusted OS for abiraterone, no significant differences between enzalutamide and abiraterone were observed either. [redacted]

Table B32 Results of the indirect comparison for OS, rPFS, time to PSA response and time to cytotoxic chemotherapy initiation – Fixed-effect model

	ENZA vs ABI HR [95% CrI]

OS	
Unadjusted ENZA OS vs ABI IA3	[redacted]
Unadjusted ENZA OS vs ABI Final	[redacted]
IPCW ENZA OS vs ABI IA3	[redacted]
IPCW ENZA OS vs ABI Final	[redacted]
rPFS	
Time to cytotoxic chemotherapy initiation	[redacted]
Time to PSA progression	[redacted]

Abbreviations: CrI: credible interval; OS: overall survival; rPFS: radiographic progression-free survival.
In bold, statistically significant outcomes.

In terms of best overall response, enzalutamide was associated with a significantly higher likelihood to lead to a complete or partial response (OR: [redacted] By contrast, no significant differences were observed between enzalutamide and abiraterone in terms of the odds to lead to progressive disease as the best overall response.

Table B33 Results of the indirect comparison for best overall response – Fixed-effect model

	ENZA vs ABI OR [95% CrI]
Best overall response	
Complete and partial response	[redacted]
Progressive disease	[redacted]

Abbreviations: CrI: credible interval; OR: odds ratio.
In bold, statistically significant outcomes.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Because the data for each pairwise treatment comparison came from single studies no statistical assessment of heterogeneity was undertaken. We have however examined possible sources of heterogeneity which could arise from:

- Comparability of the control arm in both studies
- Comparability of the patient population.

Abiraterone needs to be taken with steroids which is not the case for enzalutamide. This explains the different proportion of patients on steroids in the control arm of PREVAIL and in the COU-AA-302. As already mentioned in section 6.7.3, whether corticosteroids have any incremental benefit when given with abiraterone is not known. However, there is evidence that when given alone corticosteroids may have an impact on certain endpoints such as disease progression or burden of symptoms[5,6]. An effect on OS cannot be discarded either. Thus, exposure to corticosteroids for all patients in the control arm of COU-AA-302 study may underestimate the treatment benefit of abiraterone over placebo. Using the control

arm as the common arm in the indirect treatment comparison may also benefit enzalutamide over abiraterone. A possibility to overcome this limitation would be to adjust the indirect treatment comparison for the possible treatment effect of corticosteroids when given alone. However, current evidence does not allow us to quantify the effect of corticosteroids in chemo-naïve mHRPC patients and adjust the indirect treatment comparison.

Given the uncertainty of a potential impact of corticosteroids on the endpoints assessed in the COU-AA-302 study and after discussing this with local key opinion leaders9, the approach we have taken is to conduct a naïve direct comparison between enzalutamide and abiraterone without taking into consideration the placebo arm for the economic model. Astellas consider that the level of similitude regarding the study design, study population and endpoints of both studies allows this naïve comparison. However, the naive comparison is likely to benefit abiraterone given inclusion of patients with visceral disease in PREVAIL.

The study population of PREVAIL and COU-AA-302 studies were comparable (Table B29). Similar selection criteria were applied and both studies included asymptomatic or mildly symptomatic patients with mHRPC in whom chemotherapy is not yet clinically indicated. Despite the similarities, the proportion of patients with ECOG 1 tended to be higher in PREVAIL (ECOG 0: 68.1%; ECOG 1: 31.9%)2 than in COU-AA-302 (ECOG 0: 75.7%; ECOG 1: 24.5%)[83]. The two studies also differed in the proportion of white patients and patients with visceral disease. While only 77.1% of patients in PREVAIL were white, this percentage was 94.9% in COU-AA-302. Regarding the proportion of patients with visceral disease, while presence of visceral metastasis was an exclusion criterion in COU-AA-302, patients with lung and/or liver metastases could be enrolled in PREVAIL. Overall, 11.9% of patients in PREVAIL2 had visceral disease vs none in COU-AA-302[83].

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable as only one study was included in the ITC.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

A network-meta-analysis could not be performed due to a lack of trials that linked between different treatments and therefore no testing of inconsistency was possible.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Only one relevant non-RCT was identified in the SLR (Scher et al[54]). In Scher et al, 12 chemo-naïve patients and 12 post-chemo patients received one of the following daily doses of enzalutamide: 30, 60, 150, 240, 360, 480 and 600 mg/day. The study does not provide separate data for chemo-naïve and post-chemo patients and thus, it is not included here.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The strategy used to identify safety-related clinical studies is the same as that provided in section 6.1.1. A separate search was not conducted for AEs but AEs was considered an outcome of relevance in the systematic literature review.

The systematic review (described in sections 6.1 and 6.2) identified one RCT, PREVAIL, that collected data on AEs associated with the administration of enzalutamide in the treatment of asymptomatic or mildly asymptomatic patients with mHRPC[46].

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Safety was a secondary outcome in PREVAIL. The source for all safety data reported in this chapter is the PREVAIL Clinical Study Report2 unless stated otherwise. The PREVAIL-related safety data presented here correspond to the data cut-off date of 16 September 2013.

The overall incidence of adverse events (AEs) with enzalutamide was similar to that with placebo in PREVAIL. The nature of all grades and grade 3 or higher (≥3) AEs was comparable between arms2.

In line with longer rPFS with enzalutamide, the mean and median time on study treatment was higher in the enzalutamide arm (15.8 and 16.6 months, respectively) than in the placebo arm (7.0 and 4.6 months, respectively)2.

As expected for this patient population with advanced prostate cancer, nearly all enzalutamide- and placebo-treated patients experienced at least 1 AE in PREVAIL (Table B34). Enzalutamide-treated patients had a higher incidence of grade ≥3 events (enzalutamide: 42.9%; placebo: 37.1%) and serious adverse events (SAEs; 32.0% vs 26.8%); however, the time to first grade ≥3 event and time to first SAE were longer in the enzalutamide group compared with the placebo group. The overall incidence of AEs that were the primary reason for treatment discontinuation (enzalutamide: 5.6%; placebo: 6.0%) and AEs leading to death (enzalutamide: 4.2%; placebo: 3.8%) was similar between treatment groups2.

Table B34 Summary of adverse events in PREVAIL

Number of patients reporting ≥ 1	**ENZA (N=871)**	**PLA (N=844)**
Adverse Event	844 (96.9%)	787 (93.2%)
AE associated with study drug discontinuation	148 (17.0%)	216 (25.6%)
AE as primary reason for study drug discontinuation	49 (5.6%)	51 (6.0%)
AE leading to dose reduction of study drug	18 (2.1%)	8 (0.9%)
AE leading to temporary interruption of study drug dosing	98 (11.3%)	88 (10.4%)
AE leading to death	37 (4.2%)	32 (3.8%)
Serious adverse event	279 (32.0%)	226 (26.8%)
Median time to first serious adverse event (months) [95% CI]*	NYR [28.3, NYR]	23.3 [16.1, NYR]
Grade 3 or higher AE	374 (42.9%)	313 (37.1%)
Median time to first grade ≥3 adverse event (months) [95% CI]*	22.3 [19.0, 28.3]	13.3 [11.1, 18.2]

Source: PREVAIL Clinical Study Report2
Abbreviations: AE: adverse event; ENZA: enzalutamide; PLA: placebo.
*Based on Kaplan-Meier estimates.

Table B35 provides **all grade AEs** reported in ≥5% of patients in any arm with a ≥2% absolute difference. The AEs more commonly reported with enzalutamide than with placebo included fatigue, back pain, constipation, arthralgia, decreased appetite, diarrhoea, hot flush, asthenia, weight decrease, oedema peripheral, hypertension, headache, fall, dizziness, haematuria, insomnia, nasopharyngitis, dysgeusia, and upper respiratory tract infection. However, when the longer exposure to study drug in the enzalutamide arm was taken into account and events per 100 patient-years were calculated, only hot flush (enzalutamide: 14.0; placebo: 12.0), hypertension (enzalutamide: 11.0; placebo: 7.0), fall (enzalutamide: 11.0; placebo: 9.0) and dysgeusia (enzalutamide: 5.8; placebo: 5.7) were more commonly reported in the enzalutamide arm2.

Table B35 Adverse events (any grade) reported in ≥5% of patients in any arm with a ≥2% absolute difference in the overall rate in PREVAIL (Safety Set)

	Overall incidence, n (%)			Events per 100 patient-years of reporting, n (event rate)	
AE	**ENZA (N=871)**	**PLA (N=844)**	**RR [95% CI]**	**ENZA (N=871)**	**PLA (N=844)**
Fatigue	310 (35.6%)	218 (25.8%)	1.38 [1.19; 1.59]	353 (29.9)	233 (43.0)
Back pain	235 (27.0%)	187 (22.2%)	1.22 [1.03; 1.44]	279 (23.6)	230 (42.5)
Constipation	193 (22.2%)	145 (17.2%)	1.29 [1.06; 1.57]	218 (18.5)	154 (28.4)
Arthralgia	177 (20.3%)	135 (16.0%)	1.27 [1.04; 1.56]	219 (18.6)	160 (29.5)
Decreased appetite	158 (18.1%)	136 (16.1%)	1.13 [0.91; 1.39]	175 (14.8)	146 (27.0)
Diarrhoea	142 (16.3%)	119 (14.1%)	1.16 [0.92; 1.45]	180 (15.3)	153 (28.3)
Hot flush	**157 (18.0%)**	**65 (7.7%)**	2.34 [1.78; 3.08]	**160 (13.6)**	**66 (12.2)**
Asthenia	113 (13.0%)	67 (7.9%)	1.63 [1.23; 2.18]	149 (12.6)	72 (13.3)
Weight decreased	100 (11.5%)	71 (8.4%)	1.36 [1.02; 1.82]	102 (8.6)	74 (13.7)
Oedema peripheral	92 (10.6%)	69 (8.2%)	1.29 [0.96; 1.74]	105 (8.9)	72 (13.3)
Hypertension	**117 (13.4%)**	**35 (4.1%)**	3.24 [2.25; 4.67]	**127 (10.8)**	**36 (6.6)**
Headache	91 (10.4%)	59 (7.0%)	1.49 [1.09; 2.05]	117 (9.9)	67 (12.4)
Fall	**101 (11.6%)**	**45 (5.3%)**	2.17 [1.55; 3.05]	**128 (10.8)**	**48 (8.9)**
Dizziness	76 (8.7%)	53 (6.3%)	1.39 [0.99; 1.95]	83 (7.0)	57 (10.5)
Haematuria	73 (8.4%)	49 (5.8%)	1.44 [1.02; 2.05]	105 (8.9)	60 (11.1)
Insomnia	70 (8.0%)	47 (5.6%)	1.44 [1.01; 2.06]	74 (6.3)	47 (8.7)
Nasopharyngitis	62 (7.1%)	42 (5.0%)	1.52 [1.04; 2.23]	71 (6.0)	45 (8.3)
Dysgeusia	**66 (7.6%)**	**31 (3.7%)**	2.06 [1.36; 3.13]	**68 (5.8)**	**31 (5.7)**

	Overall incidence, n (%)			Events per 100 patient-years of reporting, n (event rate)	
AE	**ENZA (N=871)**	**PLA (N=844)**	**RR [95% CI]**	**ENZA (N=871)**	**PLA (N=844)**
Upper respiratory tract infection	53 (6.1%)	30 (3.6%)	1.71 [1.11; 2.65]	65 (5.5)	38 (7.0)

Source: PREVAIL Clinical Study Report2
Events more common with enzalutamide vs placebo after adjusting for duration of treatment are shown in bold font.

Regarding **grade ≥3 AEs**, their overall incidence was 42.9% and 37.1% for the enzalutamide and placebo arms, respectively. However, incidence of grade ≥3 AEs during the first year of treatment was lower with enzalutamide than with placebo (Table B36).

Table B36 Proportion of patients with grade ≥3 AEs in PREVAIL (Safety Set)

	ENZA (N=871)	PLA (N=844)
Patients with any grade ≥3 AE, n (%)	374 (42.9%)	313 (37.1%)
Within first 90 days	114 (13.1%)	173 (20.5%)
Within first 180 days	178 (20.4%)	251 (29.7%)
Within first 365 days	279 (32.0%)	296 (35.1%)

Source: PREVAIL Clinical Study Report2

Table B37 provides those grade ≥3 AEs reported in ≥1% of patients in any arm. Several grade ≥3 AEs were more commonly reported in the enzalutamide arm than in the placebo one. However, only hypertension (enzalutamide: 6.8%; placebo: 2.3%) was associated with an absolute difference higher than 2%.

Table B37 Adverse events grade ≥3 reported in ≥1% of patients in either group by system organ class (Safety Set)

AE	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Patients with any grade ≥3 AE	374 (42.9%)	313 (37.1%)	1.16 [1.03; 1.30]
Blood and lymphatic system disorders	37 (4.2%)	31 (3.7%)	1.16 [0.72; 1.85]
Anaemia	29 (3.3%)	25 (3.0%)	1.12 [0.66; 1.90]
Eye disorders	14 (1.6%)	2 (0.2%)	6.78 [1.55; 29.76]
Cataract	**11 (1.3%)**	**1 (0.1%)**	10.66 [1.38; 82.38]
Gastrointestinal disorders	37 (4.2%)	25 (3.0%)	1.43 [0.87; 2.36]
Nausea	**9 (1.0%)**	**4 (0.5%)**	2.18 [0.67; 7.05]
General disorders and administration site conditions	58 (6.7%)	49 (5.8%)	1.15 [0.79; 1.66]
Fatigue	16 (1.8%)	16 (1.9%)	0.97 [0.49; 1.93]
General physical health deterioration	**18 (2.1%)**	**10 (1.2%)**	1.74 [0.81; 3.76]
Asthenia	11 (1.3%)	8 (0.9%)	1.33 [0.54; 3.30]
Infections and infestations	45 (5.2%)	37 (4.4%)	1.18 [0.77; 1.80]
Urinary tract infection	13 (1.5%)	11 (1.3%)	1.15 [0.52; 2.54]
Pneumonia	**11 (1.3%)**	**7 (0.8%)**	1.52 [0.59; 3.91]
Injury, poisoning, and procedural complications	29 (3.3%)	19 (2.3%)	1.48 [0.84; 2.62]
Fall	**12 (1.4%)**	**6 (0.7%)**	1.94 [0.73; 5.14]

AE	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Musculoskeletal and connective tissue disorders	68 (7.8%)	78 (9.2%)	0.90 [0.66; 1.23]
Back pain	22 (2.5%)	25 (3.0%)	0.85 [0.48; 1.50]
Bone pain	12 (1.4%)	20 (2.4%)	0.58 [0.29; 1.18]
Arthralgia	12 (1.4%)	9 (1.1%)	1.29 [0.55; 3.05]
Pathological fracture	9 (1.0%)	7 (0.8%)	1.25 [0.47; 3.33]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	52 (6.0%)	38 (4.5%)	1.33 [0.88; 1.99]
Metastatic pain	14 (1.6%)	16 (1.9%)	0.85 [0.42; 1.73]
Nervous system disorders	73 (8.4%)	53 (6.3%)	1.33 [0.95; 1.88]
Spinal cord compression	**33 (3.8%)**	**24 (2.8%)**	1.33 [0.79; 2.23]
Syncope	**14 (1.6%)**	**8 (0.9%)**	1.70 [0.72; 4.02]
Renal and urinary disorders	49 (5.6%)	68 (8.1%)	0.70 [0.49; 1.00]
Urinary retention	8 (0.9%)	14 (1.7%)	0.55 [0.23; 1.31]
Hydronephrosis	5 (0.6%)	16 (1.9%)	0.30 [0.11; 0.82]
Haematuria	9 (1.0%)	11 (1.3%)	0.79 [0.33; 1.90]
Urinary tract obstruction	9 (1.0%)	9 (1.1%)	0.97 [0.39; 2.43]
Vascular disorders	69 (7.9%)	26 (3.1%)	2.57 [1.65; 4.00]
Hypertension	**59 (6.8%)**	**19 (2.3%)**	3.01 [1.81; 5.00]

Source: PREVAIL Clinical Study Report2
Events with at least a 0.5% absolute increased incidence with enzalutamide vs placebo are shown in bold font.

The nature of the most commonly reported **drug-related AEs** with enzalutamide was similar to that of the prominent AEs (Table B38). Fatigue and nausea were the two most commonly reported drug-related AEs in both arms. Study drug-related AEs reported with a ≥1% higher absolute incidence in the enzalutamide group included diarrhoea, constipation, fatigue, asthenia, peripheral oedema, pain in extremity, dysgeusia, headache, hot flush, flushing, and hypertension.

Table B38 Most commonly reported adverse events related to study medication in PREVAIL

System Organ Class Preferred Term	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Blood and Lymphatic System Disorders	16 (1.8%)	12 (1.4%)	1.29 [0.61; 2.71]
Anaemia	10 (1.1%)	11 (1.3%)	0.88 [0.38; 2.06]
Gastrointestinal Disorders	239 (27.4%)	206 (24.4%)	1.12 [0.96; 1.32]
Nausea	116 (13.3%)	110 (13.0%)	1.02 [0.80; 1.30]
Diarrhoea	**58 (6.7%)**	**46 (5.5%)**	1.22 [0.84; 1.78]

System Organ Class Preferred Term	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Constipation	**58 (6.7%)**	**33 (3.9%)**	1.70 [1.12; 2.58]
Vomiting	15 (1.7%)	29 (3.4%)	0.50 [0.27; 0.93]
Dyspepsia	16 (1.8%)	15 (1.8%)	1.03 [0.51; 2.08]
Flatulence	14 (1.6%)	9 (1.1%)	1.51 [0.66; 3.46]
Abdominal pain	7 (0.8%)	11 (1.3%)	0.62 [0.24; 1.58]
Dry mouth	0 (0.0%)	9 (1.1%)	0.00
General Disorders and Administration Site Conditions	306 (35.1%)	192 (22.7%)	1.54 [1.32; 1.80]
Fatigue	**220 (25.3%)**	**143 (16.9%)**	1.49 [1.24; 1.80]
Asthenia	**67 (7.7%)**	**29 (3.4%)**	2.24 [1.46; 3.43]
Oedema peripheral	**29 (3.3%)**	**16 (1.9%)**	1.76 [0.96; 3.21]
Investigations	47 (5.4%)	40 (4.7%)	1.14 [0.75; 1.72]
Weight decreased	20 (2.3%)	17 (2.0%)	1.22 [0.64; 2.30]
Metabolism and Nutrition Disorders	71 (8.2%)	61 (7.2%)	1.13 [0.81; 1.57]
Decreased appetite	62 (7.1%)	56 (6.6%)	1.07 [0.76; 1.52]
Musculoskeletal and Connective Tissue Disorders	75 (8.6%)	71 (8.4%)	1.02 [0.75; 1.40]
Arthralgia	25 (2.9%)	18 (2.1%)	1.35 [0.74; 2.45]
Myalgia	13 (1.5%)	17 (2.0%)	0.74 [0.36; 1.52]
Muscle spasms	6 (0.7%)	10 (1.2%)	0.58 [0.21; 1.59]
Pain in extremity	**14 (1.6%)**	**2 (0.2%)**	6.78 [1.55; 29.76]
Nervous System Disorders	157 (18.0%)	76 (9.0%)	2.00 [1.55; 2.59]
Dysgeusia	**47 (5.4%)**	**20 (2.4%)**	2.28 [1.36; 3.81]
Headache	**33 (3.8%)**	**17 (2.0%)**	1.88 [1.06; 3.35]
Dizziness	24 (2.8%)	17 (2.0%)	1.37 [0.74; 2.53]
Lethargy	14 (1.6%)	17 (2.0%)	0.80 [0.40; 1.61]
Paraesthesia	9 (1.0%)	3 (0.4%)	2.91 [0.79; 10.70]
Psychiatric Disorders	32 (3.7%)	17 (2.0%)	1.82 [1.02; 3.26]
Insomnia	17 (2.0%)	11 (1.3%)	1.50 [0.71; 3.18]
Reproductive System and Breast Disorders	20 (2.3%)	14 (1.7%)	1.38 [0.70; 2.72]
Gynaecomastia	14 (1.6%)	6 (0.7%)	2.26 [0.87; 5.86]
Respiratory, Thoracic, and Mediastinal Disorders	33 (3.8%)	32 (3.8%)	1.00 [0.62; 1.61]
Dyspnoea	14 (1.6%)	11 (1.3%)	1.23 [0.56; 2.70]
Skin and Subcutaneous Tissue Disorders	63 (7.2%)	37 (4.4%)	1.65 [1.11; 2.45]
Hyperhidrosis	18 (2.1%)	12 (1.4%)	1.45 [0.70; 3.00]

System Organ Class Preferred Term	ENZA (N=871)	PLA (N=844)	RR [95% CI]
Alopecia	9 (1.0%)	3 (0.4%)	2.91 [0.79; 10.70]
Dry skin	10 (1.1%)	2 (0.2%)	4.85 [1.06; 22.05]
Vascular Disorders	167 (19.2%)	68 (8.1%)	2.38 [1.82; 3.10]
Hot flush	**117 (13.4%)**	**48 (5.7%)**	2.36 [1.71; 3.26]
Hypertension	**41 (4.7%)**	**11 (1.3%)**	3.61 [1.87; 6.98]
Flushing	**15 (1.7%)**	**3 (0.4%)**	4.85 [1.41; 16.68]

Source: PREVAIL Clinical Study Report2
Abbreviation: ADR: adverse drug reaction, i.e., adverse event related to the study medication.
In bold those AEs more common in the enzalutamide arm with ≥1% absolute increase in incidence from placebo; the remaining events are either comparable between groups or more common in the placebo group.

The AEs reported for enzalutamide in PREVAIL are in line with the adverse reactions listed in the summary of product characteristics1 (Table B39).

Table B39 Adverse reactions related to enzalutamide as reported in its summary of product characteristics

MedDRA System organ class	Very common	Common	Uncommon	Unknown
Blood and lymphatic system disorders			Leucopaenia Neutropaenia	
Cardiac disorders				QT prolongation
General disorders	Asthenia Fatigue			
Injury, poisoning and procedural complications		Falls		
Musculoskeletal and connective tissue disorders		Fractures*		**Myalgia **Muscle spasms **Muscular weakness **Back pain
Nervous system disorders	Headache	Memory impairment Amnesia Disturbance in attention Restless legs syndrome	Cognitive disorder Seizure	
Psychiatric disorders		Anxiety	Visual hallucinations	
Reproductive system and breast disorder		Gynaecomastia		
Skin and subcutaneous tissue disorders		Dry skin Pruritus		
Vascular disorders	Hot flush Hypertension			

Source: Enzalutamide Summary of Product Characteristics[1]
* Includes all fractures with the exception of pathological fractures
** Spontaneous reports from post-marketing experience

Treatment with enzalutamide was associated with a clinically meaningful and statistically significant prolongation of survival in patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated, as reflected in the 29% decrease in the risk of death for patients compared with placebo (unstratified HR: 0.706; 95% CI: [0.596, 0.837]; p<0.0001).

A lower proportion of patients died due to disease progression in the enzalutamide arm than in the placebo arm (Table B40). However, a comparable proportion of patients died due to **AEs leading to death**, other causes or by unknown causes in both treatment arms. The most frequently reported AE as the cause of a fatality in both arms was general physical health deterioration (enzalutamide: N=9, 1.0%; placebo: N=4, 0.5%), followed by disease progression (enzalutamide: N=3, 0.3%; placebo: N=6, 0.7%). General physical health deterioration was likely due to disease progression. All other fatal AEs were reported in ≤2 patients in any arm except for death which was reported as the cause of the fatality in 4 and 1 patients in the enzalutamide and placebo arms, respectively2.

Table B40 Deaths and causes of deaths in PREVAIL

Deaths	**ENZA (N=872)**	**PLA (N=845)**	**RR [95% CI]**
Total number of deaths at or prior to data cut-off date	241 (27.6%)	299 (35.4%)	0.78 [0.68; 0.90]
Cause of death			
Disease progression	183 (21.0%)	227 (26.9%)	0.78 [0.66; 0.93]
Adverse event	37 (4.2%)	32 (3.8%)	1.12 [0.70; 1.78]
Other	35 (4.0%)	41 (4.9%)	0.83 [0.53; 1.28]
Unknown	23 (2.6%)	31 (3.7%)	0.72 [0.42; 1.22]
Deaths occurring ≤30 days of the first dose of study drug	1 (0.1%)	1 (0.1%)	0.97 [0.06; 15.45]
Deaths occurring ≤30 days of the last dose of study drug	35 (4.0%)	29 (3.4%)	1.17 [0.72; 1.89]

Source: Enzalutamide Summary of Product Characteristics1
Abbreviations: AE: adverse event; ENZA: enzalutamide; PLA: placebo.

Overall, 32.0% (N=279) and 26.8% (N=226) of patients in the enzalutamide and placebo arms respectively experienced at least one **SAE** of any grade or causality. The proportion of patients with SAEs during the first year of treatment was lower with enzalutamide than with placebo (Table B41). Events with at least a 0.5% absolute higher incidence in the enzalutamide arm compared with placebo were anaemia (enzalutamide: 1.6%; placebo: 0.9%), coronary artery disease (enzalutamide: 0.5%; placebo: 0.0%), fatigue (enzalutamide: 0.5%; placebo: 0.0%), femoral neck fracture (enzalutamide: 0.6%; placebo: 0.0%), pathological fracture (enzalutamide: 1.1%; placebo: 0.6%), syncope (enzalutamide: 0.7%; placebo: 0.0%), cauda equina syndrome (enzalutamide: 0.5%; placebo: 0 %) and hypertension (enzalutamide: 0.5%; placebo: 0.0%). The incidence of all other events was comparable between groups or more common in the placebo group.

Table B41 Proportion of patients with SAEs in PREVAIL (Safety Set)

	ENZA (N=871)	PLA (N=844)
Patients with any SAE, n (%)	279 (32.0%)	226 (26.8%)
Within first 90 days	57 (6.5%)	116 (13.7%)
Within first 180 days	111 (12.7%)	167 (19.8%)
Within first 365 days	193 (22.2%)	203 (24.1%)

Source: PREVAIL Clinical Study Report2

A similar proportion of patients in both treatment arms experienced an **AE that led to permanent treatment discontinuation** (enzalutamide: N=49, 5.6%; placebo: N=51, 6.0%). Those AEs that were reported in more than one patient were:

- Gastrointestinal Disorders: enzalutamide: N=4, 0.5%; placebo: N=11, 1.3%
  - Nausea: enzalutamide: N=3, 0.3%; placebo: N=3, 0.4%
  - Dysphagia: enzalutamide: N=0, 0.0%; placebo: N=3, 0.4%
  - Vomiting: enzalutamide: N=0, 0.0%; placebo: N=2, 0.2%
- General Disorders and Administration Site Conditions: enzalutamide: N=2, 0.2%; placebo: N=11, 1.3%
  - Fatigue: enzalutamide: N=2, 0.2%; placebo: N=8, 0.9%
- Injury, Poisoning, and Procedural Complications: enzalutamide: N=2, 0.2%; placebo: N=3, 0.4%
  - Subdural haematoma: enzalutamide: N=0, 0.0%; placebo: N=2, 0.2%
- Investigations: enzalutamide: N=2, 0.2%; placebo: N=2, 0.2%
  - Hepatic enzyme increased: enzalutamide: N=0, 0.0%; placebo: N=2, 0.2%
- Nervous System Disorders: enzalutamide: N=11, 1.3%; placebo: N=6, 0.7%
  - Cerebrovascular accident: enzalutamide: N=2, 0.2%; placebo: N=1, 0.1%
  - Lethargy: enzalutamide: N=0, 0.0%; placebo: N=2, 0.2%
  - Syncope: enzalutamide: N=2, 0.2%; placebo: N=0, 0.0%
- Renal and Urinary Disorders: enzalutamide: N=3, 0.3%; placebo: N=5, 0.6%
  - Renal failure acute: enzalutamide: N=2, 0.2%; placebo: N=1, 0.1%.

Regarding **significant AEs**, several of them merit special attention either because they have been identified as potential risks during the clinical program of enzalutamide or because they are events of clinical interest. These AEs are fall, non-pathological fractures, hallucination, hypertension, mental impairment, neutropenia, seizures, fatigue (and related events), gastrointestinal common events, hepatic impairment, hot flush, loss of consciousness, major cardiovascular AEs, renal impairment and venous thromboembolic events.

Table B42 Previously identified risks associated with enzalutamide (safety population)

	Overall incidence, n (%)		Events per 100 patient-years of reporting, n (event rate)	
AE	**ENZA (N=871)**	**PLA (N=844)**	**ENZA (N=871)**	**PLA (N=844)**
Potential risks				
Fall	101 (11.6%)	45 (6%)	128 (10.8)	48 (8.9)
Nonpathological fractures	68 (7.8%)	25 (3.0%)	84 (7.1)	28 (5.2)
Hallucination	1 (0.1%)	1 (0.1%)	1 (<0.1)	1 (0.2)
Hypertension-related (any hypertension event)*	121 (13.9%)	40 (4.7%)	132 (11.2)	42 (7.8)
Mental impairment	50 (5.7%)	13 (1.5%)	53 (4.5)	15 (2.8)
Neutropenia	13 (1.5%)	5 (0.6%)	20 (1.7)	6 (1.1)
Seizure	1(0.0%)†	1 (0.1%)	0 (0.0)	1 (0.2)
Other AEs of clinical interest				
Fatigue and related events (fatigue, asthenia, malaise, lethargy)	421 (48.3%)	295 (35.0%)	526 (44.6)	330 (60.9)
Gastrointestinal common events (preferred terms of nausea, vomiting, diarrhoea, constipation)	391 (44.9%)	349 (41.4%)	699 (59.2)	605 (112)
Hepatic impairment	25 (2.9%)	21 (2.5%)	38 (3.2)	29 (5.4)
Hot flush/flushing	174 (20.0%)	67 (7.9%)	179 (15.2)	69 (12.7)
Loss of consciousness (loss of consciousness and syncope)	16 (1.8%)	10 (1.2%)	16 (1.4)	10 (1.8)
Major adverse cardiovascular events#	23 (2.6%)	16 (1.9%)	24 (2.0)	16 (3.0)
Renal impairment	32 (3.7%)	38 (4.5%)	38 (3.2)	43 (7.9)
Venous thromboembolic events	15 (1.7%)	17 (2.0%)	18 (1.5)	20 (3.7)

Source: Enzalutamide Summary of Product Characteristics[1]

*Hypertension, increased blood pressure, systolic hypertension, procedural hypertension, hypertensive heart disease; †This seizure occurred after the data-cut-off date. #Major cardiovascular AEs were defined using a composite of three narrow SMQs (standardised Medical Dictionary for Regulatory Activities queries) involving myocardial infarction events, ischaemic cerebrovascular events, and haemorrhagic cerebrovascular events.

Fall and non-pathological fractures

In PREVAIL, enzalutamide was associated with a higher risk of falls and non-pathological fracture events even when adjusted for length of exposure. The majority of fall events occurred after 180 days and were grade 1 or 2 in severity. Overall,

54.4% of patients receiving enzalutamide and 44.0% receiving placebo who experienced a fracture had a fall event within the preceding 14 days. Similar to falls, the majority of events of non-pathological fracture were reported after at least 180 days of treatment in the enzalutamide group. The aetiology of the increased incidence of fall is unknown, but may be multifactorial. Age with possible contributing factors such as weakness associated with ADT, other concurrent AEs, and concomitant medication use may at least partly account for these events2. It cannot be excluded either that more common falls in the enzalutamide arm would be would be due to enzalutamide-treated patients feeling better than those in the placebo arm and are thus more active.

Hypertension

The incidence of any hypertension event was more frequent with enzalutamide versus placebo even when adjusted for length of exposure (Table B35). Events were generally reported early in both groups and easily managed with simple anti hypertensive therapy. The incidence of hypertension was 13.4% with enzalutamide versus 4.1% with placebo. Hypertension was the most common grade ≥3 AE in the enzalutamide group (6.8% vs 2.3% with placebo). No grade 4 or 5 hypertension was reported and only one enzalutamide patient (0.1%) discontinued due to hypertension2.

The majority (71.1%) of enzalutamide-treated patients with hypertension had a history of hypertension at baseline. This was also the case in the placebo arm (67.5%). The maximum mean blood pressure increase from baseline was modest (3.3 mmHg systolic and 1.7 mmHg diastolic), and observed early during treatment (Week 9), with lesser but sustained mean blood pressure increases above baseline thereafter. No relationship was observed between the higher incidence of hypertension events and subsequent events involving cardiovascular sequelae. The aetiology of hypertension associated with enzalutamide is not known2.

Mental impairment

AEs involving mental impairment (e.g. impaired cognition and memory) were more frequent with enzalutamide even when adjusted for length of exposure. However, no enzalutamide-treated patients had grade ≥3 AEs or SAEs of mental impairment versus two placebo-treated patients experiencing a grade 3 and SAE involving mental impairment. Mental impairment-related AEs were rarely a primary reason for discontinuation or dose modification in either group (enzalutamide: N=2, 0.2%; placebo: N=1, 0.1%). No relationship was observed between events involving mental impairment and clinically relevant sequelae2.

Neutropenia

Neutropenia was infrequent, but more common with enzalutamide, although grade ≥3 AEs of neutropenia (0.6% vs 0.4%) and grade ≥3 laboratory findings of neutropenia (0.9% vs 0.7%) were comparable between groups. In general, events of neutropenia were transient and not related to an increased risk of infection. Neutrophil count with enzalutamide was decreased from baseline and lower than in the placebo group at all post-baseline time points; the maximum mean absolute neutrophil count decrease from baseline was approximately 560 cells/μL at week 97 with enzalutamide. When adjusted for length of exposure, the event rate with enzalutamide remained higher than placebo2.

Seizure and hallucination

Enzalutamide was not associated with an increased risk of seizure or hallucinations in the PREVAIL study before the September 2013 data cut-off. One placebo-treated patient (0.1%) experienced a seizure event prior to this data cut-off date. In addition, one enzalutamide-treated patient (0.1%) experienced a seizure event after the data cut-off date and before database lock2. Upon further review of the medical history after the events, both patients were found to have a history of complex partial seizures, which put them at higher risk. One patient in each treatment group (0.1%) had a hallucination event. Both patients were receiving concomitant opiate medications at the time of the event.

Fatigue and related events (fatigue, asthenia, malaise, lethargy)

Fatigue along with related terms of asthenia, lethargy, and malaise were the most common AEs in PREVAIL and the overall incidence was higher with enzalutamide. However, when adjusted for the longer exposure, the event rate for fatigue and related terms was substantially lower with enzalutamide2.

The incidence of grade 3 events was equal between groups (3.0%). A lower proportion of enzalutamide-treated patients had fatigue (or related events) as the primary reason for discontinuation (0.2% vs 1.3%); but, dose reductions for fatigue (and related terms) occurred more often with enzalutamide (0.6% vs 0.1%). The aetiology of fatigue is difficult to determine as it may also be related to disease progression, progressive weakness associated with ADT, and concomitant medications commonly used as the disease advances2.

Hot flush/flushing

Hot flush and flushing were reported in a higher proportion of patients receiving enzalutamide versus placebo (20.0% vs 7.9%); however, nearly all events were grade 1–2 (only one enzalutamide-treated patient experienced a grade 3 event) and did not require discontinuation or dose modification. When adjusted for exposure, the event rate of both hot flush and flushing remained higher with enzalutamide. Hot flush and flushing occurred mostly within the first 90 days in both groups. Although hot flush is a common symptom in men receiving ADT[12], the increased incidence of hot flush associated with enzalutamide may result from a more complete inhibition of the AR signalling pathway1.

Gastrointestinal common events (nausea, vomiting, diarrhoea, constipation)

Nausea, vomiting, diarrhoea and constipation were the most frequently gastrointestinal reported AEs in PREVAIL. The incidence of nausea was comparable between groups (23.1% vs 22.5%), whereas vomiting was less frequent with enzalutamide (6.8% vs 8.3%), and constipation (22.2% vs 17.2%) and diarrhoea (16.3% vs 14.1%) more frequent. When adjusted for exposure, event rates for these common gastrointestinal events were substantially lower with enzalutamide2.

Hepatic or renal impairment

Enzalutamide was not associated with hepatotoxicity or renal toxicity upon review of AEs and laboratory studies. This lack of hepatotoxicity is distinct from other approved antiandrogens such as bicalutamide[84], nilutamide[85], and flutamide[86], as well as abiraterone4. Overall, no clinically significant or consistent finding of elevated liver function tests associated with enzalutamide was apparent in PREVAIL. A review of

laboratory data showed that mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations were generally lower with enzalutamide versus placebo at each post-baseline time point, and mean albumin and bilirubin values remained at baseline levels in both groups. Also, mean blood urea nitrogen and creatinine values were generally lower at post-baseline time points with enzalutamide versus placebo. Mean potassium levels were comparable between groups and remained at baseline. Renal function test abnormalities were rare and comparable between groups2.

Loss of consciousness

Loss of consciousness or syncope was more commonly reported with enzalutamide (1.8% vs 1.2%) but when adjusted for length of exposure, the rate was low and comparable between groups (1.4 vs 1.8 per 100 patient-years with placebo). All events of loss of consciousness with enzalutamide, and 9 of the 10 events with placebo, were grade 3. Loss of consciousness led to two enzalutamide-treated patients discontinuing and one having a dose interruption (due to syncope); no patients in either group reduced their dose as a result of loss of consciousness. Loss of consciousness events were considered serious in six patients receiving enzalutamide (0.7%) versus no placebo-treated patients2.

Major adverse cardiovascular events

An increased risk of cardiovascular events has been associated with ADT[87,88,89,90]. In PREVAIL, although the proportion of patients who had a major adverse cardiovascular event was slightly higher with enzalutamide versus placebo (2.6% vs 1.9%), when adjusted for exposure, the event rate was slightly lower with enzalutamide (2.0 vs 3.0 per 100 patient-years with placebo). In PREVAIL, cardiovascular events lead to death of 3 patients in the enzalutamide arm and 1 patient in the placebo group2.

Venous thromboembolic events

Enzalutamide was not associated with an increased risk of venous thromboembolic events. Overall, the incidence of these events was comparable between groups. The only events reported in >1 patient were deep vein thrombosis (0.9% enzalutamide vs 0.6% placebo) and pulmonary embolism (0.7% vs 1.2%)2.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In PREVAIL, the overall incidence of AEs with enzalutamide was comparable to that with placebo. The safety profile of enzalutamide 160 mg daily is considered acceptable and generally manageable with basic pharmacological treatment when needed. AEs were generally mild and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

The overall incidence of grade ≥3 and SAEs was greater with enzalutamide than with placebo however, this incidence (grade ≥3 and SAEs) was lower with enzalutamide during the first year of treatment. None of the individual SAEs were reported in more than 1.5% of patients in the enzalutamide arm, and none of the grade ≥3 in more

than 4% except for hypertension which was reported in 6.8% of patients in the enzalutamide arm2.

The most commonly reported treatment-related AEs observed with enzalutamide included fatigue and nausea. However, when adjusted for longer exposure, incidence of both AEs was lower with enzalutamide.

Based on the experience from other drugs with similar pharmacological effects, potential risk of seizure with enzalutamide was identified in its preclinical program. In PREVAIL one patient in each arm (enzalutamide: 0.1%; placebo: 0.1%) experienced a seizure. In the AFFIRM study in the post-chemo setting, this percentage was 0.9% (N=7/800) of patients in the enzalutamide arm. Seizures were generally self-limited and did not recur upon cessation of dosing2.

Currently approved therapies for asymptomatic or mildly symptomatic chemo-naïve mHRPC patients include abiraterone4 and sipuleucel-T[38]. Compared to these two treatments, enzalutamide has certain advantages:

- Unlike abiraterone4, enzalutamide does not need to be administered with corticosteroids to improve its tolerability1. This reduces the treatment burden of these patients and any possible corticosteroid-related toxicity.
- Unlike abiraterone4, enzalutamide has not been associated with hepatotoxicity or mineralocorticoid excess-related toxicity such as hypokalemia and fluid retention and thus, it does not require product specific monitoring1.
- Unlike sipuleucel-T, enzalutamide (and abiraterone) is an oral treatment1. In contrast, sipuleucel-T is administered intravenously by experienced healthcare professionals in a setting with resuscitation equipment[38]. Sipuleucel-T contains autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor). Prior to infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the sipuleucel-T bag to avoid any rejection to the infused cells.

The safety profile of enzalutamide is clearly distinct from that of abiraterone and sipuleucel-T.

In conclusion, enzalutamide is a generally well-tolerated drug. The AEs associated with enzalutamide do not put any substantial additional burden to the patient compared with BSC. This is supported by the significantly greater HRQL as assessed with FACT-P and EQ-5D in enzalutamide-treated patients.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Current management of patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated is based on BSC and

abiraterone. Although abiraterone is currently not recommended by NICE[19] patients in England have access to it through the CDF[20]. As such, abiraterone has rapidly assumed position as 'standard of care' in this group of patients in England.

The findings in PREVAIL, as well as the naïve direct comparison and the ITC versus abiraterone highlight the superiority of enzalutamide vs BSC and advantages of enzalutamide vs abiraterone in the chemo-naïve setting.

In the PREVAIL trial, enzalutamide met the co-primary endpoints (OS and rPFS) as well as all secondary and exploratory endpoints. The PREVAIL trial was a well-conducted pivotal RCT that compared enzalutamide versus placebo in the treatment of patients with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated2,3. At the time of designing this trial, BSC was the only available treatment for these patients.

Irrespective of the time of the analysis, enzalutamide significantly prolonged OS compared with placebo. In the most mature data cut-off (30 June 2014), enzalutamide reduced the risk of death by [redacted] compared with placebo. Significantly longer OS with enzalutamide was observed despite a higher proportion of patients in the placebo arm switching to therapies with the potential to prolong survival, after discontinuation of the trial medication.

In terms of rPFS, enzalutamide prolonged rPFS by 13.6 months compared with placebo (investigator assessed; 16 September 2013 data cut-off).

The superiority observed with enzalutamide for OS and rPFS was also observed for secondary and exploratory outcomes. Enzalutamide was statistically better than placebo in the radiographic tumour response, PSA response, pain palliation and HRQL.

In terms of HRQL, compared with placebo enzalutamide led to a significantly lower decrease in the FACT-P HRQL total score and all domains except for prostate cancer subscale pain related score at Week 61. Differences in favour of enzalutamide were also observed for the EQ-5D utility index and the BPI pain scores (Pain severity and Pain Interference).

Importantly, the treatment benefit of enzalutamide over placebo in PREVAIL was associated with an acceptable and manageable safety profile. AEs were generally mild and resulted in infrequent dose reductions, dose interruptions, or discontinuations.

Previously identified risks with enzalutamide include fall, non-pathological fractures, hallucination, hypertension, mental impairment, neutropenia, and seizures, however as detailed in section 6.9.2, when adjusted for the longer exposure with enzalutamide, the incidence for most of these AEs was lower with enzalutamide than with placebo. These AEs rarely led to dose reduction or permanent treatment discontinuation. One of these AEs merit special mention: seizures. Enzalutamide has been shown to increase the risk of seizure in patients with predisposing factors[91,92,93]. In PREVAIL, one patient in each arm (0.1%) experienced a seizure. However, the seizure in both arms was generally self-limited and did not recur upon cessation of dosing2.

When compared with abiraterone4, enzalutamide is associated with several advantages. Enzalutamide does not need to be administered with corticosteroids1. In

addition, routine product specific liver function, potassium and fluid balance monitoring is also not required with enzalutamide. No cases of serious liver toxicity have been reported in the phase III trials with enzalutamide and therefore, no regular liver function monitoring is required for patients on enzalutamide1. This translates into fewer clinic visits for enzalutamide-treated patients than for patients on abiraterone, with the consequence of potential cost savings. Patients on abiraterone need to have a liver function test every two weeks during the first three months and monthly thereafter4.

In conclusion, the overall efficacy and safety results support a positive benefit/risk assessment of the use of enzalutamide at a daily dose of 160 mg in adult men with asymptomatic or mildly symptomatic mHRPC in whom immediate chemotherapy is not yet clinically indicated. In PREVAIL, enzalutamide was associated with significantly better HRQL and longer time to HRQL deterioration than placebo. Better HRQL with enzalutamide is partly due to its treatment benefit on PFS and its acceptable safety profile.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Enzalutamide is the first and only androgen receptor signalling inhibitor that inhibits three steps in the signalling pathway[16]. Its strengths in the treatment of patients with symptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet clinically indicated reside in the treatment benefit observed in the co-primary, secondary and exploratory outcomes compared with placebo in PREVAIL. Enzalutamide met the co-primary outcomes as well as the secondary and exploratory outcomes. A pre-specified interim analysis after 540 deaths showed a statistically significant improvement in OS for patients treated with enzalutamide compared to placebo2. The Independent data monitoring committee recommended that the study be stopped after this interim analysis and men who received placebo be offered treatment with enzalutamide2. Significantly longer OS was observed despite a higher proportion of patients in the placebo arm being switched to therapies some of which with the potential to prolong survival after discontinuation of the trial medication. Superiority of enzalutamide over placebo in terms of OS was maintained at the most mature data cut-off and is increased when OS is adjusted for any post-study treatment discontinuation that differs from current clinical practice.

The PREVAIL trial is a high quality, robust and clinically relevant RCT which included 1,717 patients recruited at 207 sites in 22 countries in North America, Europe, Australia, and Asia2. The treatment benefit of enzalutamide has been clearly demonstrated, leading to a statistically significant delay in disease progression and HRQL deterioration with a safety profile overall acceptable and generally manageable2.

As already stated in section 6.10.1, unlike other anti-androgens, enzalutamide has not been associated with hepatotoxicity requiring routine monitoring which is a well-known toxicity of abiraterone acetate[94,95]. Enzalutamide has a safety profile distinct from abiraterone as it is not associated with mineralocorticoid excess, including hypokalemia and fluid retention[96] again with no requirement to monitor, it does not have a food effect meaning it can be taken at a time to best suit the patient rather

than having to make specific allowances in lifestyle, and does not require concomitant steroid use.

No head-to-head study comparing enzalutamide to abiraterone the main comparator for England. An ITC was attempted using the control arm of PREVAIL and COU-AA-302 but the marked differences in the control arm introduce bias to the results. However, the ITC has been conducted for an informative purpose. The results show significantly lower risk of radiographic disease progression ([redacted]), PSA progression ([redacted]), and chemotherapy initiation ([redacted],) with comparable OS to abiraterone. In addition, enzalutamide is associated with a higher likelihood to reach a complete or partial response than abiraterone ([redacted]),

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

In the UK, current management of patients with asymptomatic or mildly symptomatic mHRPC in which immediate chemotherapy is not yet clinically indicated is based on abiraterone or BSC. The latter is not currently recommended by NICE for chemo-naïve patients[19] but it is available to patients in England through the CDF[20].

The PREVAIL study is a placebo-controlled study comparing enzalutamide to placebo. Management of patients in the placebo arm is the equivalent to BSC. No head-to-head study comparing enzalutamide with abiraterone has been conducted in the chemo-naïve setting. In order to assess the relative efficacy of enzalutamide to that of abiraterone in this setting, an ITC has been conducted. However, as already highlighted in section 6.7.2, the ITC is not appropriate to compare the relative efficacy of enzalutamide vs abiraterone due to the markedly different use of steroids in the control arm of both studies used in the ITC.

At present, there is no curative treatment for mHRPC. At the advanced stages of prostate cancer, the aim of new medicinal products is to prolong survival and offer palliation without compromising the patient's HRQL. Taking this into account, EMA[60] and FDA[61,62] consider OS and PFS as the most relevant endpoints to be assessed in clinical studies with new anticancer medicinal products in man. In addition, both entities recommend to assess the ORR or tumour stabilisation as a secondary endpoint[60,61,62]. EMA state that when no curative treatment exists, patient reported outcomes or HRQL are relevant outcomes that need to be measured[60]. In the latest guidance for clinical trials with new anticancer drugs EMA issue specific recommendations for clinical studies in mHRPC[60]. These recommendations also highlight the relevance of OS and PFS in mHRPC.

In PREVAIL, enzalutamide resulted in statistically and clinically significant longer OS and rPFS. Significantly longer rPFS translated into longer exposure to treatment in the enzalutamide arm compared with the placebo arm. Despite longer exposure, enzalutamide was associated with better HRQL as assessed by the FACT-P and EQ-5D. Similarly, compared to placebo enzalutamide significantly delayed time to first

deterioration of HRQL by 5.3 months when assessed by FACT-P, by 8.1 months when assessed with the EQ-5D utility index score and by 8.3 months when assessed with EQ-5D VAS score. The favourable HRQL observed in patients treated with enzalutamide resulted in a gain of +0.03 utilities when compared with placebo. Better HRQL with enzalutamide is partly due to its treatment benefit on PFS and its acceptable and generally manageable safety profile.

At study entry patients were asymptomatic or mildly symptomatic. Enzalutamide was associated with significantly fewer patients with pain progression when assessed with the pain severity composite score (41.0% vs 50.5%; p<0.001), pain at its worst (item #3 of the BPI; 41.0% vs 49.4%; p=0.002) or pain interference composite score (31.3% vs 41.6%; p<0.001). Similarly, enzalutamide was associated with significantly smaller increase in the severity of pain (+0.52 vs +0.79) and pain interference with daily activities (+0.58 vs +0.99) between baseline and Week 25. In these patients, pain is due mainly to metastases to the bone and worsens with disease progression. It is a burdensome symptom that requires specific treatment with analgesics and opioids in a significant proportion of patients.

The outcomes assessed in PREVAIL (OS and rPFS as co-primary outcomes, and radiographic tumour response, time to first SRE, changes in PSA, HRQL, pain and safety as secondary outcomes) are relevant for the indication of interest in this submission and are aligned with EMA and FDA recommendations.

In conclusion, the clinical endpoints in PREVAIL are consistent to those specified in the decision problem and therefore can be considered applicable to UK clinical practice. For further information regarding the relevance of the endpoints assessed please refer to section 6.3.5.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The use of enzalutamide in PREVAIL reflects its intended use in clinical practice. The efficacy, safety profile and tolerability expected for enzalutamide in real life clinical practice are the same as those observed in the PREVAIL trial.

The manufacturer does not anticipate that the study results observed in the PREVAIL trial will differ from those with its use in UK clinical practice. A substantial proportion of patients in the PREVAIL trial were enrolled in the UK (N=153; 8.9%), reinforcing that the clinical benefits and safety profile demonstrated in the PREVAIL trial are not likely to differ from those expected in UK clinical practice.

7 Cost-effectiveness

Key points

- This economic analysis evaluated the cost-effectiveness of enzalutamide compared with abiraterone and BSC for the treatment of adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.
- This revised submission dossier uses manufacturer's list prices for enzalutamide and abiraterone in place of the existing Patient Access Scheme discounts, at the request of NICE. The results should be interpreted with caution.
- A Markov model was developed with three health states: stable disease, progressed disease and death, which can be considered to be the standard economic modelling approach in oncology[97]. However, given that patients may receive further lines of treatment after disease progression, three treatment states were nested in the progressed disease health state: post-progression 1 (PP1), post-progression 2 (PP2) and palliative care. AEs and SREs were included in the model.
- Key inputs for OS and time on treatment were derived from the PREVAIL study of enzalutamide and the COU-AA-302 study of abiraterone. Given the differences described in sections 6.7.2 and 6.7.9 between the control arms of both studies an adjusted ITC is statistically inappropriate; Therefore, a naive comparison of treatment effect was carried out between enzalutamide and abiraterone without taking into consideration the control arm of either study. However, it is likely that differences in the patient populations of PREVAIL and COU-AA-302, namely the inclusion in PREVAIL of patients with visceral disease, introduce bias against enzalutamide in a naive comparison.
- Treatment discontinuation in PREVAIL was considered the best proxy for disease progression (and thus discontinuation) in clinical practice. Oncologists actively treating prostate cancer in the UK confirmed that the decision to discontinue treatment is not made on a single measure of progression alone (e.g. rPFS)[43,44,]9 and that patients in clinical practice would discontinue according to the same criteria as in the trial, or even before all trial discontinuation criteria are met9. This endpoint has previously been accepted by NICE[43,44]. However, given that no time to treatment discontinuation has been published for patients on abiraterone in COU-AA-302, rPFS is used for abiraterone in the model. In PREVAIL, the rPFS and TTD endpoints were comparable. Median rPFS was 19.7 months for enzalutamide and 5.4 months for placebo, and median TTD was 17.7 months for enzalutamide and 4.6 months for placebo[81]. Given that PREVAIL and COU-AA-302 used comparable criteria for discontinuation of study drug, the difference between rPFS and TTD for abiraterone is also expected to be small.
- Unlike the 3rd interim analysis of COU-AA-302, in PREVAIL a wide range of life extending treatments were available for patients to receive following discontinuation of study drug. Many of these treatments are not available in UK clinical practice and are associated with an impact on OS. Statistical adjustment of the impact of therapies received 2nd line (that is ahead of docetaxel) on OS has been carried out on the ITT population (30 June 2014) of PREVAIL using the IPCW method. It was not possible to adjust for the use of therapies outside of UK clinical practice that were received 3rd line or later; more frequently received in the placebo arm. Consequently, the relative OS benefit of enzalutamide may be underestimated versus BSC.

- The Weibull parametric distribution was found to be the most plausible estimate of OS for both the IPCW adjusted enzalutamide KM curve and the 3rd interim analysis of abiraterone in the COU-AA-302 trial.
- AEs and SREs have been individually accounted for in the model by using rates of each event from PREVAIL and applying associated costs and disutilities derived from the literature. Incidences for the selected AEs for abiraterone were taken from the Rathkopf publication (third interim analysis)[82] and the abiraterone FDA label[111]. As only AEs of special interest were reported in Rathkopf et al[82], AE rates for the abiraterone arm may be underestimated. No information on SREs were available from COU-AA-302; therefore, it was conservatively assumed that SREs would be equivalent for patients treated with abiraterone and enzalutamide.
- The base case incremental cost effectiveness ratio (ICER) for enzalutamide was £27,076per QALY gained against abiraterone and £78,587per QALY gained against BSC.
- Extensive scenario analyses and deterministic and probabilistic sensitivity analysis showed that the model was robust, and that enzalutamide is a cost-effective treatment option versus either comparator. The probabilistic sensitivity analysis (PSA) showed an 59% probability of enzalutamide being cost-effective against abiraterone at a willingness to pay (WTP) of £30,000 per QALY gained. A scenario analysis to review the cost-effectiveness of enzalutamide taking into account the Pharmaceutical Price Regulation Scheme (PPRS) was included. Under this scheme, overspend on expenditure on branded medicines is repaid to the Department of Health by PPRS member companies. As the PPRS guarantees the NHS budget for medicines, it represents a key factor to be taken into account when assessing whether use of a particular treatment represents good use of NHS resources. The 2015 payment percentage of 10.36% was applied in a scenario analysis. This scenario resulted in an ICER of £23,642/QALY vs abiraterone compared to the base case ICER of £27,076/QALY. The ICER of this scenario was £69,911/QALY vs BSC, compared to the base case ICER of £78,587/QALY.

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A SLR was carried out to retrieve any relevant data from the published literature regarding the cost-effectiveness of enzalutamide and relevant comparators as outlined in the scope[46]. The search strategy for economic studies is detailed in Appendix 10, section 10.10. The databases searched are listed in Table B43. In addition, the searches were supplemented with hand searching of the bibliographies

of relevant review articles, conference proceedings and trial databases, and with unpublished data from the manufacturer.

No date or language limits were applied during the search. However, studies with English abstracts but whose full reports were in languages other than English were not eligible for extraction and were listed for information only.

Table B43 Databases searched for economic studies relevant to the decision problem

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
EMBASE	OvidSP
EconLit	OvidSP
NHS Economic Evaluation Database (NHS EED)	http://www.crd.york.ac.uk/crdweb/
Health Economic Evaluation Database (HEED)	EBSCOHost
Cost-Effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4/Home.aspx
Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)	http://www.proqolid.org/
Health Technology Assessment Database (HTA Database)	http://www.crd.york.ac.uk/crdweb/
Scottish Medicines Consortium (SMC)	http://www.scottishmedicines.org.uk/Home
Pharmaceutical Benefits Advisory Committee (PBAC)	http://www.pbs.gov.au/pbs/home
NICE	http://www.nice.org.uk/
Pan-Canadian Oncology Drug Review (pCODR)	http://www.pcodr.ca/wcpc/portal/
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/en
Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)	http://www.tlv.se/

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No cost-effectiveness study assessing enzalutamide in the chemo-naïve setting was identified in the systematic literature review. However, an economic study in the chemo-naïve setting has been reviewed for this submission and is summarised in Table B44.

Table B44 Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
Manufacturer submission for abiraterone in the chemo-naïve setting[35]	2013	England and Wales	The model is an individual time-to-event simulation or discrete event simulation The model includes three phases: pre-docetaxel, docetaxel and post-docetaxel.	Adult men (≥18 yrs) who have asymptomatic or mildly symptomatic mHRPC after failure of ADT in whom chemotherapy is not yet clinically indicated Median age was 70 years	QALYs for intervention and comparator are not published as they are commercial in confidence Incremental QALYs: +0.57 QALYs	Costs are provided in GBP sterling pounds. Total costs for intervention and comparator are not published as they are commercial in confidence Incremental costs when the PAS is applied: +£26,404	ICER when the PAS is applied: £46,722

ICER, incremental cost-effectiveness ratio; mHRPC, metastatic hormone relapsed prostate cancer; PAS, patient access scheme; QALY(s), quality-adjusted life year(s)

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[‡] or Philips et al. (2004)[§]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

The quality assessment is provided in section 10.11.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient group considered in the economic model is the overall patient population in the PREVAIL study which is: "adult men with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated" (section 6.3.3). This is the same population as the licensed indication1 (section 1.5).

Model structure

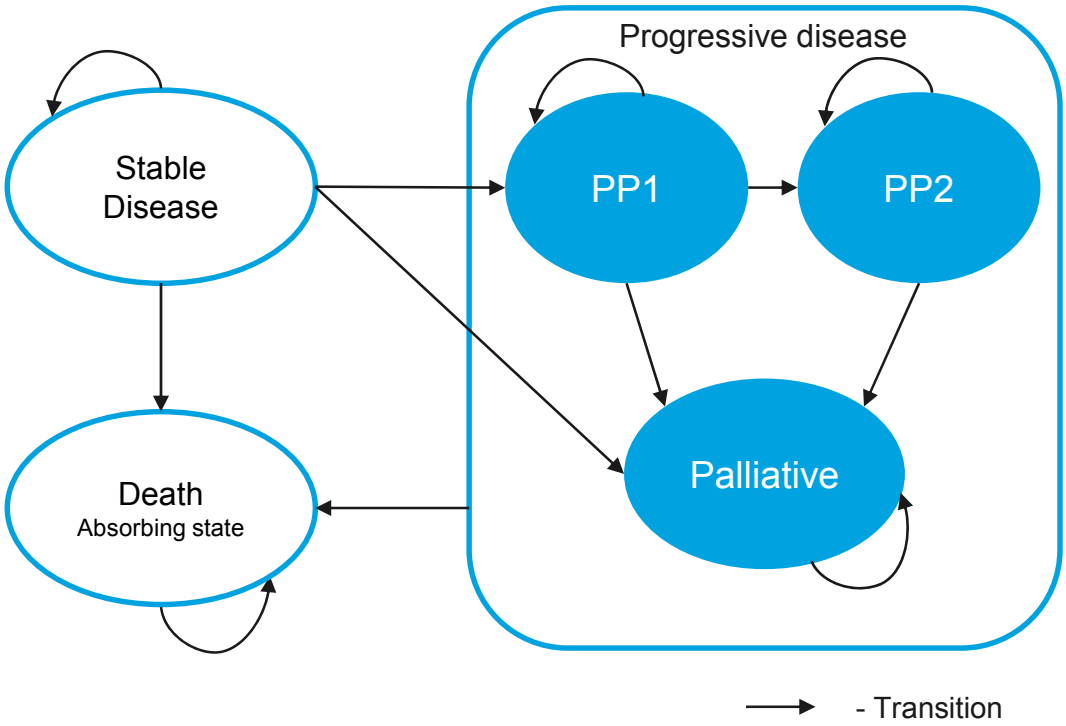
7.2.2 Please provide a diagrammatical representation of the model you have chosen.

[‡] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[§] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

The model for enzalutamide in the chemo-naive setting is graphically illustrated in Figure B17 and described in section 7.2.3.

Figure B17 Model structure of the enzalutamide economic model



Abbreviations: PP1: post-progression 1; PP2: post-progression 2

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

A Markov model has been chosen as the most appropriate, transparent and efficient way to model mHRPC pathway. In line with previous models in mHRPC[42,43], a model with three health states: stable disease, progressed disease and death; was used (Figure B17). However, using a single progressed disease health state to mimic several different therapies in the presence of different allowable sequences based on initial treatment, will inevitably lead to greater imprecision. Such imprecision is exacerbated when extrapolation is required.

A similar approach of incorporating further lines of post-progression treatment in order to accurately reflect a natural history of a disease was successfully used in the imatinib submission to NICE[98].

Current clinical guidelines and clinical practice in the UK indicate that patients are likely to receive additional active treatments once their disease has progressed. The duration of treatments received after disease progression and subsequent costs and QoL impact are important aspects for accurate modelling. Therefore, the progressed disease health state was divided into three treatment states:

- Post-progression 1 (PP1): this state includes mHRPC patients who are alive, have progressed from stable disease (i.e., the equivalent to progression-free

health state) and moved on to a 2nd line of treatment but have not yet further progressed
- Post-progression 2 (PP2): this state includes mHRPC patients who are alive, have progressed on their PP1 treatment and have moved to a 3rd line of treatment but have not yet further progressed
- Palliative care: this state includes mHRPC patients who have progressed and receive palliative care (no active treatment).

Metastatic HRPC patients enter the model in the Stable Disease health state having received prior ADT. They remain in this health state as long as they remain alive and progression free. Patients who die move to the death health state, whilst patients who progress move to the PP1 or Palliative therapy treatment state. Patients in the PP1 treatment state remain in this treatment state until their disease progresses (and they move on to PP2 or Palliative therapy) or die (and move to the Death health state). Patients in PP2 remain in this treatment state until their disease progresses (and they move on to Palliative therapy) or die (and move to the Death health state). Patients in Palliative therapy remain in this treatment state until they die. Patients are at risk of death in each cycle, regardless of which health state/treatment state they reside in. Overall, the following transitions are possible:

- From the Stable Disease to PP1, Palliative therapy or Death
- From PP1 to PP2, Palliative therapy or Death
- From PP2 to Palliative therapy or Death
- From Palliative therapy to Death.

Transitions between health states in the model are defined by the OS and time on treatment curves for each treatment, further described in section 7.3.1. The probability of dying (whilst residing in Stable Disease or Progressed Disease is defined as 1 minus the probability of remaining alive (1-OS), and the probability of moving from Stable Disease to Progressed Disease is defined as the probability of remaining alive minus the probability of remaining progression free (OS-PFS).

The model compares the intervention enzalutamide, with the comparators stated in the decision problem (section 5), i.e., abiraterone and BSC.

When patients enter the model they can receive enzalutamide, BSC or abiraterone (Table B45). In PP1, all patients receive docetaxel. Other PP1 options have been available in the clinical trial settings but were corrected for as they are not approved in the UK. Upon progression following docetaxel treatment only patients in the BSC arm can receive another active treatment. This is in line with clinical practice in the UK where prescription of enzalutamide or abiraterone is not recommended if patients have received any of these two treatments previously[99]. Thus, patients who received enzalutamide or abiraterone when they enter the model will only receive palliative care upon progression following treatment with docetaxel.

Table B45 Model treatment pathway

	Treatment arm		
Health state	**ENZA arm**	**BSC arm**	**ABI arm**
Stable Disease	Enzalutamide	BSC	Abiraterone
PP1	Docetaxel	Docetaxel	Docetaxel
PP2	N/A	Enzalutamide*	N/A
Palliative	Palliative treatment	Palliative treatment	Palliative treatment
Death			

*Please note, in the model all patients moving to PP2 receive enzalutamide instead of a proportion of enzalutamide and abiraterone for simplicity. A scenario analysis with abiraterone given after docetaxel in the BSC arm is undertaken to test the impact.

7.2.4 Please define what the health states in the model are meant to capture.

Given that HRQL decreases upon progression (further defined in section 7.3.1), it is important to distinguish between Stable Disease and the different treatment states within the Progressed Disease health state. In the Stable Disease health state patients remain on treatment until the disease progresses. In this health state patients are asymptomatic or mildly symptomatic but may experience AEs (grade 3 and higher) which will have a negative impact on the patient's HRQL.

Progression in mHRPC is typically associated with bone metastasis[63,31]. In these patients bone metastases can grow rapidly and cause debilitating complications known as SREs (e.g. spinal cord compression, pathological bone fracture)[100,101]. SREs have a marked impact on HRQL[102,103] and thus they are implemented in the model.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model captures patients with mHRPC who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated. As discussed in section 2.1, mHRPC is a severe condition, with a poor survival and a large impact on HRQL. The model captures these aspects as it evaluates both survival and HRQL of these patients. Both positive effects (treatment) and negative effects (progression, AEs, SREs) on HRQL are included.

All patients are assumed to be stable upon starting treatment, and receive enzalutamide, BSC or abiraterone (Stable Disease). The treatment is continued until

disease progression when patients will move to the next line of treatment or directly to palliative care. The model therefore captures the important distinction between the pre-progression (Stable Disease) and post-progression states (PP1, PP2 and Palliative therapy), and includes events that may have a potentially large impact on HRQL (AEs, SREs).

The natural disease evolution of patients with mHRPC who are asymptomatic or mildly symptomatic and in whom chemotherapy is not yet clinically indicated is illustrated in the BSC arm of the model. Patients in this arm remain in the Stable Disease state until progression.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B46 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime horizon implemented as 10 years	This time horizon is assumed to be sufficient to capture the remaining life time of a mHRPC patient, as the median survival in phase III clinical trials for both enzalutamide and abiraterone did not exceed 36 months.	PREVAIL[37], COU-AA-3028
Cycle length	1 week	This allows for sufficient detail in the model calculations taking into account a monitoring frequency of 2-8 weeks.	
Half-cycle correction	Applied to LY, QALY, and all costs except direct drug costs, chemotherapy administration costs and concomitant medications costs	A half cycle correction is applied to correct for the fact that patients move between health states continuously instead of at distinct time points. This correction was not applied to direct drug costs, chemotherapy administration costs and concomitant medications costs to reflect potential wastage.	NICE guide to the methods of technology appraisal 2013[104]
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference case	NICE guide to the methods of technology appraisal 2013[104]
Discount of 3.5% for utilities and costs	Yes	NICE Reference case	NICE guide to the methods of technology

Factor	Chosen values	Justification	Reference
			appraisal 2013[104]
Perspective (NHS/PSS)	The NHS and personal social services (PSS) in the UK	NICE Reference case	NICE guide to the methods of technology appraisal 2013[104]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Dosage and administration of enzalutamide1 and abiraterone4 are implemented in the model as per their marketing authorisations.

The placebo arm of PREVAIL was assumed to represent BSC2,3. Patients in the placebo arm could receive LHRH analogues (if not surgically castrated), corticosteroids, blood transfusions, bisphospohonates, radiotherapy, analgesics and palliative surgery to treat SREs, when needed2.

Conversely, it is inappropriate to consider the placebo arm of COU-AA-302[82,83,8] to represent BSC. This is because, all patients in COU-AA-302 were required to receive corticosteroids (prednisolone 10mg per day) to maintain the blind nature of randomisation[82,83]. In the active arm of COU-AA-302 (abiraterone arm), all patients had to receive corticosteroids to reduce CYP17 related toxicity (hypertension, hypokalaemia and fluid retention).

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

No treatment continuation rule has been assumed in the model. However, the model does assume that patients continue treatment up to progression or death (whichever comes first). As progression can be difficult to quantify (as definitions may differ between studies, or as trial definitions may not resemble clinical practice), treatment discontinuation from the trial was considered the best proxy to determine the treatment duration in clinical practice (discussed in detail in section 7.3.1).

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Clinical data for the BSC and enzalutamide arms were derived from the PREVAIL study2. The placebo arm of PREVAIL received no active treatment but was allowed supportive treatments (section 7.2.7), and was therefore assumed to represent BSC. Data inputs for OS, TTD, AEs, SREs and proportion of patients moving to subsequent treatments were derived from this trial. Abiraterone data were derived from the COU-AA-302 study[82], and a naive comparison was used to compare the treatment effects of enzalutamide and abiraterone (section 6.7.9).

Survival curves for OS and TTD were derived following the recommendations of the NICE DSU guidance on survival modelling[105], and are described in detail in the following sections:

- First the proportionality of hazards assumption was tested to see whether it was appropriate to use the HR
  - Individual curves were used if the proportionality of hazards assumption was not met
- Parametric models were fitted to each treatment arm
  - Five different survival models (Exponential, Weibull, Log-Logistic, Log-Normal and Generalised Gamma) were fitted to the patient level data
  - The most plausible model was selected based on:
    - Face validity
    - Clinical validity of the tail and extrapolated estimates (performed by clinical experts)
    - Statistical fit using Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC)

7.3.1.1 Overall survival

The PREVAIL study was unblinded after the planned interim analysis at the data cut-off date of 16 September 2013 (section 6.5.3). As many patients were still alive at the end of the study, extrapolation was required in order to estimate the outcomes over a lifetime time horizon. As extrapolation is associated with uncertainty, the most mature OS data is preferred for economic modelling[72]. Therefore, for the purpose of the economic model, an additional data cut was analysed at a cut-off date of 30 June 2014. At the cut-off date of 30 June [redacted] had occurred in the enzalutamide group and [redacted] had occurred in the placebo group. Please note, no death sweep (i.e., validation of survival status at time of cut-off) was performed for the 30 June 2014 data cut-off.

As noted earlier, in PREVAIL, as of 30 June 2014 cut-off date, [redacted] in the placebo arm and [redacted] in the enzalutamide arm received a 2nd line post-study drug treatment that patients would not have received in clinical practice[37] (Table B22; section 10.15.1). Such therapies included abiraterone, enzalutamide, cabazitaxel and sipuleucel-T.

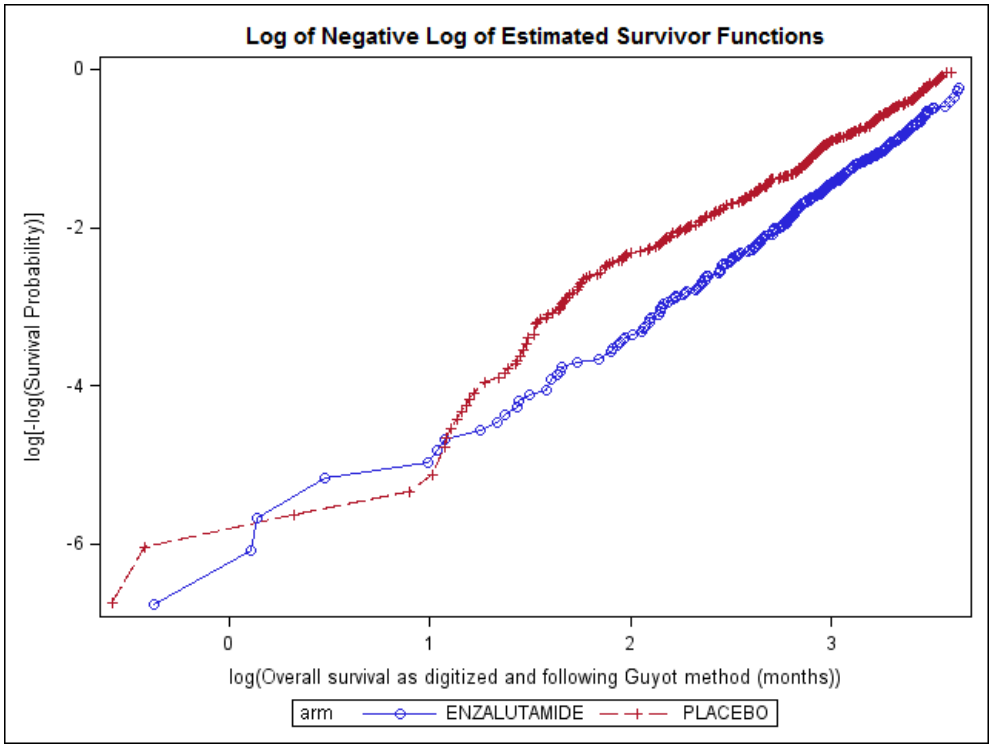
The standard ITT analysis (i.e. all randomised patients) is likely to underestimate the "true" OS benefit associated with the study drug when more patients in the comparator arm switch to treatments that are known to prolong survival and therefore

benefit from the drug they have been switched to. This will affect the cost-effectiveness analyses which make use of the OS evidence[71]. As discussed in Section 6.3.6.6, two methods for adjustment for treatment switching (defined as switching to 2nd line treatments which are not part of the standard treatment pathway in the UK) have been applied: IPCW and two-stage method. The decision to use the IPCW method for the economic base case was based on its stronger theoretical background, and clinical plausibility of assumptions. However, the two-stage method is used in a scenario analysis (7.7.10).

The IPCW method provides an adjusted hazard ratio and a weighted Kaplan Meier (WKM) curve; it does not provide patient-level data for standard extrapolation models to be applied. Therefore the method provided by Guyot et al (2012)[108] was used to generate individual patient data. The IPCW method does not provide the number of patients at risk at the different timepoints. Guyot et al (2012) indicate in their paper that the performance of the algorithm is poor when no number of patients at risk are available. We have therefore assumed the same number of patients at risk as in the ITT analysis. It is important to note that the WKMs associated with the IPCW are not adjusted for baseline covariates, unlike the IPCW-adjusted HR (Table B24).

For the purposes of extrapolation the validity of assuming proportional hazards in the OS data was investigated by plotting log (-log [estimated survival distribution function]) against log (survival time) of the adjusted OS data. In the presence of proportional hazards, the hazard ratio would be applied to the reference (BSC) curve; however, in the absence of proportional hazards, separate curves are generally applied to model the survival of each treatment arm. Graphical inspection of the loglog curves indicated that the hazards were not proportional over the entire follow-up period. However, in the adjusted dataset, convergence of the survival curves did not occur until towards the end of the follow-up period (Figure B18). It was considered that this may be at least partly a result of differences in 3rd line treatments received by patients in the enzalutamide and BSC arms. That is, patients in the BSC arm would receive 3rd line treatment (not adjusted for using either the IPCW or two-stage methods) with a known survival benefit, more frequently and earlier than patients in the enzalutamide arm.

Figure B18 Graphical inspection of the loglog curves



Five parametric distributions were fitted individually to enzalutamide and placebo arms to the reconstructed individual patient data after digitizing the WKM from the IPCW adjustment: Exponential, Weibull, Log-Logistic, Log-Normal and Generalised Gamma.

Statistical goodness-of-fit was assessed based on the AIC and BIC: smaller values indicating a better fit. Examination of the results presented in Table B47 reveals that the lowest AIC/BIC values are those obtained from the Gamma and Weibull distributions for both enzalutamide and BSC arms. Table B47 also reveals that the AIC/BIC values of the Weibull distribution are only marginally larger than the values of the Gamma distribution. The corresponding parameter estimates of the distributions are presented in Table B48.

Table B47 Goodness of fit for PREVAIL OS – IPCW (June 2014 cut-off)

	PLA		ENZA	
Distribution	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: PREVAIL extrapolation report[81]
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Numbers in bold indicate the best fit.

Table B48 Maximum likelihood parameter estimates for PREVAIL OS – IPCW (June 2014 cut-off)

Treatment	Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Placebo	Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape (SE)	[redacted]	[redacted]			[redacted]
Enzalutamide	Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape (SE)	[redacted]	[redacted]			[redacted]

Source: PREVAIL extrapolation report[81]
Abbreviations: SE: standard error

It should be noted that the SEs obtained from the parametric models will be underestimated because it does not take into account the fact that patients have had their survival times transformed by the IPCW method. Although it is recommended to use bootstrapping for the parametric fitting[106,107], given the large number of parametric models, and the use of the Guyot method, this was not practically possible. The lack of bootstrapping will not affect the base case, but may underestimate uncertainty in the probabilistic sensitivity analysis.

The Kaplan-Meier plot along with estimates from the parametric models are presented in Appendix A (Figure A.3. 11) of the PREVAIL extrapolation report (section 10.15.2). These figures describe the OS curve fitting functions for both placebo and enzalutamide at both the early phase of the curves (up to 36 months) and across the entire curves. Visual examination of these figures revealed that both the Weibull and the Gamma distribution provide adequate fit to the observed data.

The clinical plausibility of the OS outcome after adjustment for treatment switching using the IPCW method was assessed by considering the percentage of patients alive at 5 and 10 years, provided in Table B49. No external data sources on survival in mHRPC could be identified to externally validate the extrapolation estimates for OS.

Table B49 Estimated percentages of patients alive at 5 and 10 years – PREVAIL IPCW analysis (June 2014 cut-off)

	PLA		ENZA	
Distribution	**5-year**	**10-year**	**5-year**	**10-year**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: PREVAIL extrapolation report[81]

Examination of the extrapolation plots[81] (section 10.15.2), revealed that when using the Gamma distribution for both arms, the two curves cross after [redacted] months. When applying the Weibull distribution, curves also cross but this occurs at a much later stage (at about [redacted] months when only [redacted] of patients are alive.). Whilst the crossing of curves is problematic, the alternative parametric functions produce implausible five and ten-year survival estimates.

Clinical experts considered that any crossing of the curves is not realistic; however, the proportions of patients alive at 5 and 10 years obtained from the Weibull extrapolation were considered to be more reasonable than those obtained when using Gamma curves. Therefore, evaluating all the criteria for the model selection and taking into account the clinical plausibility of the distribution tail, the Weibull distribution was selected as the best fit for the OS outcome after adjustment for treatment switching using the IPCW method for both treatment arms.

It is important to note that the use of the proportional hazards assumption would avoid the crossing of the survival curves, thereby providing a potentially more clinically plausible extrapolation. A scenario describing proportional hazards has been presented in section 7.7.10.

As described in section 6.7.9, a naive comparison was used to compare enzalutamide and abiraterone. A naive comparison was selected over the adjusted ITC as experts considered that a naive comparison would be likely to be less biased. Also an adjusted indirect comparison was considered statistically inappropriate. However, it is important to note that as a result of assuming equivalence between placebo and placebo plus prednisone, the ITC is likely to underestimate the treatment effect of abiraterone versus BSC. By contrast, differences in the patient population and concomitant medication received by patients in PREVAIL and COU-AA-302 are likely to result in underestimation of the relative treatment effect of enzalutamide versus abiraterone in a naive comparison.

In the COU-AA-302 study three interim analyses were planned for OS: the first analysis – after 116 of the required 773 events (15%), the second analysis – after 311 events (40%), and the third analysis - after 425 events (55%); a final analysis was planned for after 773 events had occurred[83]. The final analysis was published two weeks prior to this submission and has therefor not been incorporated into the economic analysis. Moreover, the curves available from the final anlaysis are subject to crossover bias; whereas cross-over at the time of the 3rd interim analysis was minimal. As the curves were needed for fitting parametric survival functions, and given that the curves adjusted for the effect of cross-over are not available, the 3rd interim analysis was used for the model.

In order to model survival for patients on abiraterone the following approach was taken:

- The Kaplan-Meier curves from COU-AA-302 study - 3rd interim analysis[82] were digitised using Engauge Digitizer 5.1
- Individual patient data were reconstructed from the Kaplan-Meier curves and the reported numbers at risk using the method published by Guyot 2012[108]
- Parametric models were fit to the abiraterone Kaplan-Meier curve, and directly applied in the model.

As patient level data from COU-AA-302 were not available, nor adjusted survival curves were published, it was not possible to adjust abiraterone OS data for treatment switching.

Statistical goodness-of-fit was assessed based on the AIC and BIC: smaller values indicating a better fit. Examination of the results presented in Table B50 reveals that the lowest AIC/BIC values are those obtained from the Gamma followed by Log-logistic distributions. Table B50 also reveals that the AIC/BIC values of the Weibull distribution are only marginally larger than the values of the Gamma distribution.

The digitised Kaplan-Meier plot along with estimates from the parametric models are presented in Appendix 17 (section 10.17). These figures describe the OS curve fitting functions for the abiraterone arm at both the early phase of the curves (up to 36 months) and across the entire curves. Visual examination of these figures revealed that all three distributions (Weibull, Log-Logistic and the Gamma distribution) provide adequate fit to the observed data.

The parameter estimates of the distributions are presented in Table B51. Importantly, the parameter value for the Log-Logistic model for the abiraterone arm is >1 (Table B51) indicating initially an increasing hazard, followed by a decreasing hazard, which was not considered plausible in the longer term. Data from other mCRPC studies[79,80] support an assumption of a monotonically increasing hazard, such as the Weibull distribution.

In addition, guidance included in the NICE DSU technical support document[105] suggests that generally it is likely to be most appropriate to avoid fitting vastly different functional forms to patients who have the same underlying disease. To provide consistency with OS modelling for enzalutamide, we have therefore selected the Weibull distribution for the economic base case for the abiraterone arm. The Gamma distribution is presented in a scenario analysis (Section 7.7.10).

Table B50 Goodness of fit for abiraterone OS

	ABI +PRED	
Distribution	**AIC**	**BIC**
Exponential	943.0	947.3
Weibull	860.6	869.2
Log-Normal	861.5	870.1
Log-Logistic	859.3	867.9
Gamma	**858.8**	**867.4**

Source: goodness of fit of OS Kaplan-Meier curves from COU-AA-302 (3rd IA)[82]
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Numbers in bold indicate the best fit

Table B51 Parameter estimates for abiraterone OS

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	4.16 (0.07)	3.71 (0.04)	3.60 (0.05)	3.55 (0.05)	3.67 (0.06)
Scale (SE)	1.00 (0.00)	0.51 (0.03)	0.85 (0.05)	0.45 (0.03)	0.67 (0.12)
Shape (SE)	1.00 (0.00)	1.00 (0.00)			0.52 (0.32)

Source: parametric fits of OS Kaplan-Meier curves from COU-AA-302 (3rd IA)[82]
Abbreviations: SE: standard error

7.3.1.2 Progression free survival

PFS is a common endpoint in oncology trials. However, definitions differ between trials, and indications.

The PREVAIL protocol included rPFS as a measure of progression and was measured at weeks 9, 17, 25, and then every 12 weeks thereafter. However, rPFS was not selected for the purpose of the health economic model because it does not accurately reflect how disease progression (and treatment discontinuation) would be defined in UK clinical practice. UK experts indicated that patients in clinical practice would not get the same frequency of scans as in PREVAIL and that the decision to

discontinue treatment would not be made on a single measure of disease progression[32].

In contrast to rPFS, treatment discontinuation in PREVAIL was a continuous process. In addition, the decision to discontinue treatment in PREVAIL was based on a combination of criteria as patients received their assigned therapy until disease progression was documented and confirmed (i.e., confirmed radiographic progression or the occurrence of a SRE) and the patient was scheduled to initiate another systemic antineoplastic therapy. Therefore, the TTD endpoint was considered a more accurate reflection of clinical practice for modelling purposes and was used to model progression from Stable Disease to Progressed Disease. TTD has already been used in previous NICE assessments and accepted by NICE[32].

TTD data were available for the cut-off date of June 2014, and in the base case these data were used to inform the modelled time on treatment with enzalutamide and with BSC[**]. Proportionality of hazards, as assessed by loglog plots, was not met. Because of this and several additional factors including statistical curve fit, face validity and predictive validity, the base case TTD for enzalutamide and BSC was modelled using separate curves. Five distributions were considered: Exponential, Weibull, Log-Logistic, Log-Normal, and Gamma.

Examination of the results presented in Table B52 reveals that the lowest AIC/BIC values are the Log-normal for placebo and Log-Logistic for enzalutamide. However, the Weibull and Gamma distribution also provide a reasonable fit to the observed data as shown by the similar AIC/BIC values. The corresponding parameter estimates of the distributions are presented in Table B53.

Table B52 Goodness of fit for PREVAIL TTD (June 2014 cut-off)

	PLA		ENZA	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: PREVAIL extrapolation report[81] (section 10.15.2)
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Numbers in bold indicate the best fit

[**] Please note that rPFS is applied to abiraterone because the TTD for abiraterone in COU-AA-302 has not been published.

Table B53 Maximum likelihood parameter estimates for PREVAIL TTD (June 2014 cut-off)

Treatment	Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Placebo	Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape (SE)	[redacted]	[redacted]			[redacted]
Enzalutamide	Intercept (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scale (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Shape (SE)	[redacted]	[redacted]			[redacted]

Source: PREVAIL extrapolation report[81] (section 10.15.2)
Abbreviations: SE: standard error

The Kaplan-Meier plot along with estimates obtained from the parametric models are presented in Appendix A (Figure A.3. 5) of the PREVAIL extrapolation report (section 10.15.2). Visual examination of these figures revealed that all distributions except for the Exponential provide adequate fit to the data.

The clinical plausibility for the TTD outcome was assessed. The percentage of patients still on the study drug at 3 and 5 years is provided in Table B54 below.

Table B54 Estimated percentages of patients still on study drug at 3 and 5 years – PREVAIL TTD analysis (June 2014 cut-off)

	PLA		ENZA	
Distribution	**3-year**	**5-year**	**3-year**	**5-year**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Source: PREVAIL extrapolation report[81] (section 10.15.2)

Examination of the results in Table B54 revealed that using the Log-logistic or Log-normal distributions, it is estimated that [redacted] of patients would still take enzalutamide 5 years after the start of the model. This was not considered reflective of clinical practice; moreover it was considered implausible that [redacted] of the [redacted] of patients estimated by the Weibull extrapolation to be alive (Table B49 - details are provided in the PREVAIL extrapolation report [section 10.15.2)] at 5 years would be on 1st line treatment. A more plausible result is provided by the Gamma distribution (3rd best statistical fit) where about [redacted] of patients are still on enzalutamide 5 years after diagnosis. This assumption has been validated with clinical experts during the Advisory Board meeting that took place in October 2014[9]. It should be noted that the difference between the Gamma distribution and the Log-logistic distribution in the AIC/BIC statistic is marginal (Table B52). Therefore, the Gamma distribution was selected for the TTD data to be used in the economic base case for both the enzalutamide and BSC arms.

As described in section 6.7.9, as a result of the impact of steroids on OS and especially PFS, a naive comparison was used to compare enzalutamide and abiraterone. As TTD has not been reported in the COU-AA-302 study[82], the Kaplan-Meier rPFS curves were digitised using Engauge Digitizer 5.1. In PREVAIL, the rPFS and TTD endpoints were close: median rPFS was 19.7 months for enzalutamide and

5.4 months for placebo, median TTD was 17.7 months for enzalutamide and 4.6 months for placebo[81]. Therefore, given that PREVAIL and COU-AA-302 used comparable criteria for discontinuation of study drug, the difference between rPFS and TTD for abiraterone is also expected to be small. The impact of using rPFS vs TTD has been explored in a scenario analysis (section 7.7.10). Estimates of individual patient level data obtained from the digitisation were then reconstructed from the Kaplan-Meier curves and the reported numbers at risk using the method published by Guyot et al[108]. For the purposes of extrapolation, a variety of parametric models were fitted to the reconstructed individual patient data, with the Gamma distribution used in the base case to provide consistency with progression modelling for enzalutamide. The digitised Kaplan-Meier plot along with estimates from the parametric models are presented in Appendix 17 (section 10.17). These figures describe the rPFS curve fitting functions for the abiraterone arm at both the early phase of the curves (up to 36 months) and across the entire curves.

Examination of the results presented in Table B55 reveals that the lowest AIC/BIC values are those obtained from the Gamma distribution. The Gamma extrapolation of rPFS with abiraterone from COU-AA-302 was then directly applied in the model. The parameter estimates of the distributions are presented in Table B56.

Table B55 Goodness of fit for abiraterone rPFS

	ABI	
Distribution	**AIC**	**BIC**
Exponential	1,285.21	1,289.51
Weibull	1,273.87	1,282.48
Log-Normal	1,247.55	1,256.16
Log-Logistic	1,255.55	1,264.15
Gamma	**1,246.96**	**1,255.57**

Source: goodness of fit of rPFS Kaplan-Meier curves from COU-AA-302 (3rd IA)[82]
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; Numbers in bold indicate the best fit

Table B56 Parameter estimates for abiraterone rPFS

Parameter	Exponential	Weibull	Log-Normal	Log-Logistic	Gamma
Intercept (SE)	3.16 (0.06)	3.12 (0.05)	2.74 (0.06)	2.74 (0.05)	2.66 (0.12)
Scale (SE)	1.00 (0.00)	0.84 (0.04)	1.12 (0.05)	0.65 (0.03)	1.15 (0.06)
Shape (SE)	1.00 (0.00)	1.00 (0.00)	-	-	-0.18 (0.23)

Source: parametric fits of rPFS Kaplan-Meier curves from COU-AA-302 (3rd IA)[82]
Abbreviations: SE: standard error

7.3.1.3 Moving to PP1

The proportions of patients moving to the PP1 treatment state (versus moving to the palliative care treatment state) for enzalutamide and BSC were calculated using data from PREVAIL. By June 2014 all patients receiving placebo had discontinued treatment, whereas only 73.3% of the patients treated with enzalutamide had discontinued. Therefore, the more mature data from the placebo arm of PREVAIL were used to inform the proportion of patients moving onto 2nd line treatment, regardless of treatment arm. Of the 844 patients initially randomised to placebo in PREVAIL, 713 (84.5%) took any post-baseline treatment (details are provided in the

PREVAIL OS Adjustment report (section 10.15.1). This estimate is in line with feedback from UK experts, who suggested that the majority of patients would receive docetaxel after discontinuing enzalutamide, BSC or abiraterone9. So this proportion was used for enzalutamide, abiraterone and BSC treatment arms.

7.3.1.4 Discontinuation of post-progression treatment

The probabilities of discontinuing post-progression treatments (exiting the PP1 and PP2 treatment states) were based on the median treatment durations reported in key clinical trials (Table B57). For enzalutamide and abiraterone, the post-chemotherapy trials of AFFIRM and COU-AA-301 were used. The per cycle probabilities of discontinuing were calculated from the median durations. Patients receiving palliative care are assumed to remain in the palliative care treatment state until death.

Table B57 Probability to discontinue from PP1 or PP2

Treatment	Median treatment duration (months)	Probabilities to discontinue per cycle (week)	Source
Docetaxel	6.58 (9.5 cycles)	0.024	TAX 327[109]
Enzalutamide	8.3	0.019	AFFIRM[11]
Abiraterone	7.4	0.021	COU-AA-301 (Fizazi 2012)[110]

Abbreviations: PP1: post-progression 1; PP2: post-progression 2

7.3.1.5 Proportion Moving to PP2

In the base case, patients in the BSC arm are eligible for a 3rd-line of active treatment (PP2 treatment state). Similar to the proportions of patients moving from PP1 to PP2, data from the placebo arm of PREVAIL is used to estimate the proportion of patients moving on to receive 3rd line active treatment. Of the 387 patients who stopped docetaxel as 2nd line, 313 (80.9%) patients went on to receive 3rd line treatment.

7.3.1.6 Adverse events

Rates of AEs for enzalutamide and BSC were gathered from the PREVAIL trial. In line with previous submissions to NICE[32], the model incorporated the most commonly occurring AEs with a severity ≥ grade 3 and an incidence ≥2% for any treatment group.

AE rates for enzalutamide and BSC were calculated based on the number of patients with each AE in PREVAIL and the treatment emergent period (total patient years, 1,180.1 for enzalutamide and 541.6 for placebo).

Abiraterone incidences for the selected AEs were taken from the Rathkopf publication[82] and the abiraterone FDA label[111]. Rates were calculated from the number of patients with each AE in the treatment emergent period (patient years). As the treatment emergent period was not reported in the COU-AA-302 study[82], it was assumed to be the same as in PREVAIL (total patient years, 1,180.1 for abiraterone and 541.6 for placebo plus prednisone). The rate difference was calculated for abiraterone vs prednisone, and this difference was added to the PREVAIL placebo AE rates, assuming that difference between control arms does not affect difference in AE rates. In reality however, all patients in the COU-AA-302 study were on steroids;

therefore, the model could underestimate steroid related AEs for the abiraterone arm. The model could also underestimate AEs for the abiraterone arm as only grade 3-4 AEs of special interest were reported in Rathkopf et al[82].

Docetaxel incidences for the selected AEs were taken from the Tannock publication[109]. Similarly to abiraterone, the model could underestimate AEs for patients treated with docetaxel as only grade 3-4 AEs of special interest were reported in Tannock et al[109].

AEs are applied using a cycle probability of each AE calculated from the AE rates in the individual trials.

Durations of AEs were based on the values reported in the abiraterone post-chemo ERG report[137].

The number of patients with a grade ≥ 3 AE in each trial and the calculated rates are shown in Table B58. In total, 12 AEs were incorporated in the model.

Table B58 Number of patients with grade ≥3 AEs and rates used in model

	PREVAIL2				COU-AA-302 (Rathkopf 2014[82]; FDA label[111])						ITC	TAX327[109]	
	ENZA		PLA		ABI		PLA		ABI-PLA		ABI-ENZA	Docetaxel	
AE	n (pts)	Rate (per pt-year)	n (pts)	Rate (per pt-year)	n (pts)	Rate (per pt-year)	n (pts)	Rate (per pt-year)	RD	SE RD	Indirect rate	n (pts)	Rate (per pt-year)
Anaemia	29	0.02	25	0.05		0.00		0.00	0.00	0.00	0.00	17	0.09
Arthralgia	0	0.00	0	0.00	11	0.01	11	0.02	-0.01	0.01	0.00		0.00
Back pain	22	0.02	25	0.05		0.00		0.00			0.00		0.00
Bone pain	12	0.01	20	0.04		0.00		0.00			0.00		0.00
Deterioration in general physical health	18	0.02	10	0.02		0.00		0.00			0.00		0.00
Dyspnoea	0	0.00	0	0.00	13	0.01	5	0.01	0.00	0.01	0.00		0.00
Fatigue	0	0.00	0	0.00	13	0.01	10	0.02	-0.01	0.01	0.00	17	0.09
Febrile neutropenia	0	0.00	0	0.00		0.00		0.00	0.00	0.00	0.00	10	0.05
Hypertension	59	0.05	19	0.04	23	0.02	17	0.03	-0.01	0.01	0.02		0.00
Hypokalaemia	0	0.00	0	0.00	14	0.01	10	0.02	-0.01	0.01	0.00		0.00
Neutropenia	0	0.00	0	0.00		0.00		0.00	0.00	0.00	0.00	106	0.58
Oedema Peripheral/Fluid retention	0	0.00	0	0.00	5	0.00	9	0.02	-0.01	0.01	0.00		0.00
Total	140	0.12	99	0.18	79	0.07	62	0.11	-0.05	0.04	0.11	150	0.81

Abbreviations: AE: adverse event; ENZA: enzalutamide; PLA: placebo; ABI: abiraterone; n: number; pts: patients; pt: patient; ITC: indirect treatment comparison; RD: rate difference

7.3.1.7 Skeletal related events

SREs are a key aspect of mHRPC and may have a big impact on a patient's HRQL and costs. The model includes the following SREs: spinal cord compression, pathological bone fractures, radiation to the bone, and surgery to the bone. It should be noted that this is a slightly different definition from that used in the PREVAIL protocol; change of antineoplastic therapy to treat bone pain was not considered a SRE in the model because it has only cost implications and this is already covered with treatment costs. Change of antineoplastic therapy has no implication on utility values.

The number of SREs during Stable Disease was extracted from the PREVAIL trial data (Table B59). SRE rates for enzalutamide and BSC were calculated based on the number of events and the treatment emergent period (patient-years, 1,149.7 for enzalutamide and 494.9 for placebo in Stable Disease health state; 1,572.2 for enzalutamide and placebo post-progression).

As no information on SREs in patients treated with abiraterone in the chemo-naïve setting was available, it was conservatively assumed that abiraterone shows the same probability of experiencing a SRE as enzalutamide. One of the well known side effects of long-term steroid use is bone loss or osteroporosis, a key cause of SREs[112,113]. Although no data are available regarding incidence of SREs for patients on abiraterone in the chemo-naïve setting, because of the needs of prescribing steroids with abiraterone to reduce its mineralocorticoid-related toxicity it is likely that SREs incidence in abiraterone-treated patients is higher than in patients on enzalutamide. In addition to this, key opinion leaders stated that incidence of SREs is higher in patients treated with abiraterone than in patients on enzalutamide9.

For post-progression (PP1, PP2 and palliative care treatment states) one SRE rate was used regardless of the treatment arm. Therefore the numbers of patients with an SRE from the AFFIRM and COU-AA-301 study was pooled for more accurate estimation of SRE rates (Table B60).

Table B59 Number and rates for SREs in PREVAIL (Stable Disease)

Event	Number of SREs		SRE rate	
	ENZA	PLA	ENZA	PLA
Spinal cord compression	38	21	0.033	0.042
Pathological bone fracture	41	15	0.036	0.030
Radiation to the bone	130	83	0.113	0.168
Surgery to the bone	15	9	0.013	0.018
TOTAL	224	128	0.195	0.259

Abbreviations: ENZA: enzalutamide; PLA: placebo; SRE: skeletal related event

Table B60 Pooled number and rates for SREs for enzalutamide, abiraterone and placebo in AFFIRM and COU-AA-301 (PP1, PP2 and palliative care treatment states)

Event	Number of SREs	SRE rate
Spinal cord compression	176	0.112
Pathological bone fracture	100	0.064
Radiation to the bone	586	0.373
Surgery to the bone	39	0.025
TOTAL	901	0.573

Abbreviations: SRE: skeletal related event

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were calculated from the survival curves described in section 7.3.1.The survival curves used in the model are summarised in Table B61.

Table B61 Survival curves used for each arm for OS and TTD/PFS

Comparator Outcome	BSC	Enzalutamide	Abiraterone
OS	Adjusted (IPCW) Weibull parametric fit of PREVAIL OS data enzalutamide arm	Adjusted (IPCW) Weibull parametric fit of PREVAIL OS data placebo arm	Weibull parametric fit of COU-AA-302 OS data abiraterone arm
TTD/rPFS	Gamma parametric fit of PREVAIL TTD data enzalutamide arm	Gamma parametric fit of PREVAIL TTD data placebo arm	Gamma parametric fit of COU-AA-302 rPFS data abiraterone arm

Abbreviations: BSC: best supportive care; OS: overall survival; TTD: time to treatment discontinuation; rPFS: radiographic progression free survival; IPCW: inverse probability of censoring weights

The cumulative hazard *H(t)* $H(t)$and the survival function *S(t)* $S(t)$for the Weibull parametric fit can be defined as follows:

$$H(t) = \lambda t \wedge \gamma$$

$$S(t) = \exp(-\lambda t \wedge \gamma)$$

The lambda (λ) and gamma (γ) were calculated from the intercept and scale parameters reported in section 7.3.1 using: λ=exp (-intercept/scale) and γ=1/scale.

The cumulative hazard *H(t)* and the survival function *S(t)* for the Gamma parametric fit can be defined as follows:

$$H(t) = -LN(1 - GAMMADIST(z, \alpha, 1, TRUE)$$

$$S(t) = \exp(LN(1 - GAMMADIST(z, \alpha, 1, TRUE))$$

The integration point for the Gamma distribution (*z*) was calculated based on the shape parameter reported in section 7.3.1 and v using: *z*=1/shape^2*v^shape.

A transformation based on mu and sigma (v) was calculated from the intercept and scale parameters reported in section 7.3.1 using: v=exp((LN(t)-intercept)/scale).

Alpha (α) was calculated from the shape parameter reported in section 7.3.1 using: α=1/shape^2

The transition probability for a given value of t can then be calculated using the formulas shown below, assuming a cycle length *u*.

$$tp(t) = 1 - \{H(t-u) - H(t)\}$$

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Yes, transition probabilities for OS and PFS vary over time as defined by the survival curves.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No intermediate outcome measures were not linked to final outcomes. OS and PFS were modelled using independent survival curves.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[††]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A series of face-to-face advisory boards were held to validate the health economic model and its inputs[9,114]. For each advisory board clinical experts and health economic experts were invited to participate. Clinical experts were selected based on their experience with mHRPC and consisted of clinical oncologists, radiologists, and urologists. Experts from the UK participated in all advisory boards including the meeting held on 29 October 2014 which focused on the economic model to be submitted to NICE. Seven UK experts participated in the NICE-specific Advisory Board.

The assumptions employed in the health economic model were made in a manner consistent with the published literature and previous NICE appraisals. These

[††] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

assumptions were then presented at the advisory board, as well as the clinical results from the PREVAIL study. Feedback from the advisory boards was incorporated in the health economic model and presented at the final advisory board (NICE specific) in October 20149.

Clinical parameters validated by the clinical experts include (but are not limited to) the plausibility of the parametric fits for OS and PFS, the applicability of rPFS and TTD, similarity of discontinuation (TTD) criteria in clinical trials, similarity between treatment discontinuation in clinical trial and clinical practice and the model structure.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B62 Summary of variables applied in the economic model

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
General inputs			7.2.6
Cycle length (wks)	1	N/A	
Time horizon (years)	10	No distribution assumed, assumed CI: [5; 15]	
Discount rate for costs	3.5%	No distribution assumed, assumed CI: [0; 5]	
Discount rate for effects	3.5%	No distribution assumed, assumed CI: [0; 5]	
Average body area for patients on chemotherapy	2.01	N/A	NICE ERG report on cabazitaxel [42]
Proportion of pts moving to PP1 and PP2			10.15.1
% of progressed patients who receive 2nd line treatment after 1st line ENZA	84.5%	Beta distribution, SE assumed 10% of mean	
% of progressed patients who receive 2nd line treatment after 1st line BSC	84.5%	Beta distribution, SE assumed 10% of mean	
% of progressed patients who receive 2nd line treatment after 1st line ABI	84.5%	Beta distribution, SE assumed 10% of mean	
% of patients moving to 3rd line ENZA after progression of 2nd line treatment	80.9%	Beta distribution, SE assumed 10% of mean	
Maximum duration of docetaxel given as 1st line therapy	10	No distribution assumed, assumed CI: [1; 10]	NICE. Prostate cancer: diagnosis and treatment. Clinical guideline CG175[31]
Median treatment duration	6.58	Lognormal, SE = 0.13	Based on median

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
of docetaxel (months)			number of docetaxel cycles 9.5 (Tannock 2004[109])
Median treatment duration of ENZA given after docetaxel (months)	8.30	Lognormal, SE = 0.04	Based on median time on treatment (Scher 2012[11])
Costs (£)			7.5
Treatment (costs per cycle)			7.5.5
BSC	0	N/A	
ENZA	97.67	N/A	
ABI	97.67	N/A	
Concomitant medication (costs per cycle)			7.5.5
BSC	6.93	Gamma distribution, SE assumed 10% of mean	
Enzalutamide	6.86	Gamma distribution, SE assumed 10% of mean	
Abiraterone	7.15	Gamma distribution, SE assumed 10% of mean	
Docetaxel	71.65	Gamma distribution, SE assumed 10% of mean	
Costs of chemotherapy administration (costs per cycle)	100.8	Gamma distribution, SE assumed 10% of mean	NHS reference costs 2012-2013[142]
Health state costs (costs per cycle)			7.5.5
BSC	36.47	Gamma distribution, SE assumed 10% of mean	
ENZA			
First three months	34.66	Gamma distribution, SE assumed 10% of mean	
Subsequent months	20.91	Gamma distribution, SE assumed 10% of mean	
ABI		Gamma distribution, SE assumed 10% of mean	
First three months	64.55	Gamma distribution, SE assumed 10% of mean	
Subsequent months	36.26	Gamma distribution, SE assumed 10% of mean	
Docetaxel	73.87	Gamma distribution, SE assumed 10% of mean	
Palliative care	103.82	Gamma distribution, SE assumed 10% of mean	
Terminal treatment (transition cost)	3,598	Gamma distribution, SE assumed 10% of mean	7.5.6
Hospitalisations (costs per cycle)	0	N/A	7.5.6
Utility			7.4
Stable Disease	0.844	Beta distribution, SE: 0.0039	7.4.3
PP1	0.658	Beta distribution, SE: 0.0065	7.4.9
PP2	0.612	Beta distribution, SE: 0.0242	7.4.9

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
Palliative	0.500	Beta distribution, SE: 0.08	7.4.9
Utility benefit on treatment			7.4.3
ENZA	0.022	Normal distribution, SE: 0.009	
ABI	0.022	Normal distribution, SE: 0.009	
ENZA given after docetaxel	0.04	Normal distribution, SE: 0.004	
Overall survival			
OS BSC	Weibull Intercept = [redacted] Scale = [redacted]	Multivariate Normal	PREVAIL, data on file 7.3.1.1
OS ENZA	Weibull Intercept = [redacted] Scale = [redacted]	Multivariate Normal	PREVAIL, data on file 7.3.1.1
OS ABI	Weibull Intercept = [redacted] Scale = [redacted]	Multivariate Normal	7.3.1.1 COU-AA-302 (3rd IA[82])
PFS			
PFS BSC	Gamma Intercept = [redacted] Scale = [redacted] Shape = [redacted]	Multivariate Normal	PREVAIL, data on file 7.3.1.2
PFS ENZA	Gamma Intercept = [redacted] Scale = [redacted] Shape = [redacted]	Multivariate Normal	PREVAIL, data on file 7.3.1.2
PFS ABI	Gamma Intercept = [redacted] Scale = [redacted] Shape = [redacted]	Multivariate Normal	7.3.1.2 COU-AA-302 (3rd IA[82])
Disutility for AEs			7.4.8
Anaemia	-0.12	Normal distribution, SE = 0.047	
Arthralgia	-0.07	Normal distribution, SE = 0.012	
Back pain	-0.07	Normal distribution, SE = 0.012	
Bone pain	-0.07	Normal distribution, SE = 0.012	
Deterioration in general physical health	-0.13	Normal distribution, SE = 0.03	
Dyspnoea	-0.05	Normal distribution, SE = 0.012	
Fatigue	-0.13	Normal distribution, SE = 0.03	
Febrile neutropenia	-0.12	Normal distribution, SE = 0.016	
Hypertension	-0.15	Normal distribution, SE = 0.049	
Hypokalaemia	0.00	Normal distribution, SE = 0	
Neutropenia	-0.09	Normal distribution, SE = 0.015	

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
Oedema Peripheral/Fluid retention	0.00	Normal distribution, SE = 0	
Duration of AEs (in days)			7.4.8
Anaemia	10.50	No distribution assumed, assumed CI: [7; 14]	
Arthralgia	10.50	No distribution assumed, assumed CI: [7; 14]	
Back pain	10.50	No distribution assumed, assumed CI: [7; 14]	
Bone pain	10.50	No distribution assumed, assumed CI: [7; 14]	
Deterioration in general physical health	91.25	No distribution assumed, assumed CI: [21; 180]	
Dyspnoea	10.50	No distribution assumed, assumed CI: [7; 14]	
Fatigue	91.25	No distribution assumed, assumed CI: [21; 180]	
Febrile neutropenia	10.50	No distribution assumed, assumed CI: [7; 14]	
Hypertension	10.50	No distribution assumed, assumed CI: [7; 14]	
Hypokalaemia	10.50	No distribution assumed, assumed CI: [7; 14]	
Neutropenia	10.50	No distribution assumed, assumed CI: [7; 14]	
Oedema peripheral/ fluid retention	10.50	No distribution assumed, assumed CI: [7; 14]	
AE rates ENZA			7.3.1.6
Anaemia	0.02	Lognormal, SE = 0.19	
Arthralgia	0.00	N/A	
Back pain	0.02	Lognormal, SE = 0.21	
Bone pain	0.01	Lognormal, SE = 0.29	
Deterioration in general physical health	0.02	Lognormal, SE = 0.24	
Dyspnoea	0.00	N/A	
Fatigue	0.00	N/A	
Febrile neutropenia	0.00	N/A	
Hypertension	0.05	Lognormal, SE = 0.13	
Hypokalaemia	0.00	N/A	
Neutropenia	0.00	N/A	
Oedema Peripheral/Fluid retention	0.00	N/A	
AE rates BSC			7.3.1.6
Anaemia	0.05	Lognormal, SE = 0.20	
Arthralgia	0.00	N/A	
Back pain	0.05	Lognormal, SE = 0.20	
Bone pain	0.04	Lognormal, SE = 0.22	
Deterioration in general physical health	0.02	Lognormal, SE = 0.32	
Dyspnoea	0.00	N/A	
Fatigue	0.00	N/A	
Febrile neutropenia	0.00	N/A	
Hypertension	0.04	Lognormal, SE = 0.23	
Hypokalaemia	0.00	N/A	

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
Neutropenia	0.00	N/A	
Oedema Peripheral/Fluid retention	0.00	N/A	
AE abiraterone rate difference vs BSC			7.3.1.6
Anaemia	0.00	N/A	
Arthralgia	-0.01	Normal, SE = 0.01	
Back pain	0.00	N/A	
Bone pain	0.00	N/A	
Deterioration in general physical health	0.00	N/A	
Dyspnoea	0.002	Normal, SE = 0.01	
Fatigue	-0.01	Normal, SE = 0.01	
Febrile neutropenia	0.00	N/A	
Hypertension	-0.01	Normal, SE = 0.01	
Hypokalaemia	-0.01	Normal, SE = 0.01	
Neutropenia	0.00	N/A	
Oedema Peripheral/Fluid retention	-0.01	Normal, SE = 0.01	
AE rates docetaxel			7.3.1.6
Anaemia	0.09	Lognormal, SE = 0.24	
Arthralgia	0.00	N/A	
Back pain	0.00	N/A	
Bone pain	0.00	N/A	
Deterioration in general physical health	0.00	N/A	
Dyspnoea	0.00	N/A	
Fatigue	0.09	Lognormal, SE = 0.24	
Febrile neutropenia	0.05	Lognormal, SE = 0.32	
Hypertension	0.00	N/A	
Hypokalaemia	0.00	N/A	
Neutropenia	0.58	Lognormal, SE = 0.1	
Oedema Peripheral/Fluid retention	0.00	N/A	
Costs for AEs (£)			7.5.7
Anaemia	1,779	Gamma, SE based on IQR = 602	
Arthralgia	176	Gamma, SE based on IQR = 80	
Back pain	467	Gamma, SE based on IQR = 4	
Bone pain	606	Gamma, SE based on IQR = 174	
Deterioration in general physical health	12	Gamma, SE based on IQR = 249	
Dyspnoea	0	Gamma, SE based on IQR = 4	
Fatigue	12	Gamma, SE based on IQR = 0	
Febrile neutropenia	4,519	Gamma, SE based on IQR = 4	
Hypertension	433	Gamma, SE based on IQR = 2044	

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
Hypokalaemia	348	Gamma, SE based on IQR = 143	
Neutropenia	161	Gamma, SE based on IQR = 122	
Oedema Peripheral/Fluid retention	914	Gamma, SE based on IQR = 339	
SRE Disutilities			7.4.2
Spinal cord compression	-0.24	Normal distribution, SE = 0.079	
Pathological bone fracture	-0.20	Normal distribution, SE = 0.080	
Radiation to the bone	-0.06	Normal distribution, SE = 0.021	
Surgery to the bone	-0.06	Normal distribution, SE = 0.021	
SRE duration (in days)			7.4.2
Spinal cord compression	30.42	No distribution assumed, SA range: 0-213	
Pathological bone fracture	30.42	No distribution assumed, SA range: 0-213	
Radiation to the bone	30.42	No distribution assumed, SA range: 0-213	
Surgery to the bone	30.42	No distribution assumed, SA range: 0-213	
Costs for SREs (£)			7.5.7
Spinal cord compression	4,688	Gamma, SE based on IQR = 2,605	
Pathological bone fracture	5,351	Gamma, SE based on IQR = 1,322	
Radiation to the bone	683	Gamma, SE based on IQR = 126	
Surgery to the bone	3,568	Gamma, SE based on IQR = 1,696	
SRE rate ENZA Stable Disease			7.3.1.7
Spinal cord compression	0.033	Lognormal, SE = 0.162	
Pathological bone fracture	0.036	Lognormal, SE = 0.156	
Radiation to the bone	0.113	Lognormal, SE = 0.088	
Surgery to the bone	0.013	Lognormal, SE = 0.258	
SRE rate BSC Stable Disease			7.3.1.7
Spinal cord compression	0.042	Lognormal, SE = 0.218	
Pathological bone fracture	0.030	Lognormal, SE = 0.258	
Radiation to the bone	0.168	Lognormal, SE = 0.110	
Surgery to the bone	0.018	Lognormal, SE = 0.333	
SRE rate ABI Stable Disease			7.3.1.7
Spinal cord compression	0.033	Lognormal, SE = 0.162	
Pathological bone fracture	0.036	Lognormal, SE = 0.156	
Radiation to the bone	0.113	Lognormal, SE = 0.088	
Surgery to the bone	0.013	Lognormal, SE = 0.258	
SRE rate ENZA post-progression			7.3.1.7
Spinal cord compression	0.112	Lognormal, SE = 0.075	

Variable	Value	Distribution / 95% CI	Source / Reference to section in submission
Pathological bone fracture	0.064	Lognormal, SE = 0.100	
Radiation to the bone	0.373	Lognormal, SE = 0.041	
Surgery to the bone	0.025	Lognormal, SE = 0.160	
SRE rate BSC post-progression			7.3.1.7
Spinal cord compression	0.112	Lognormal, SE = 0.075	
Pathological bone fracture	0.064	Lognormal, SE = 0.100	
Radiation to the bone	0.373	Lognormal, SE = 0.041	
Surgery to the bone	0.025	Lognormal, SE = 0.160	
SRE rate ABI post-progression			7.3.1.7
Spinal cord compression	0.112	Lognormal, SE = 0.075	
Pathological bone fracture	0.064	Lognormal, SE = 0.100	
Radiation to the bone	0.373	Lognormal, SE = 0.041	
Surgery to the bone	0.025	Lognormal, SE = 0.160	

Abbreviations: AE: adverse events; BSC: best supportive care; ENZA: enzalutamide; ABI: abiraterone CI: confidence interval; HR: hazard ratio; PFS: progression free survival; SRE: skeletal related event; OS: overall survival; SE: standard error; wks: weeks; yrs: years.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

As not all patients in PREVAIL had progressed or died at the end of the study, extrapolation was required. As described in section 7.3.1, clinical outcomes are extrapolated beyond the trial follow-up duration by fitting parametric curves to the observed data. OS for BSC, enzalutamide and abiraterone was shown to be best described by a Weibull distribution, and TTD - by a Gamma distribution. A comparison of curve fittings to Kaplan-Meier plots is provided in Appendix A (Figure A.3. 11 for OS, Figure A.3. 11 for TTD) of the PREVAIL extrapolation report[81] (section 10.15.2).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B63 Assumptions in the economic model

Assumption	Justification	Reference
The population of PREVAIL is reflective of the UK	PREVAIL only included asymptomatic or mildly symptomatic patients with progressive mHRPC who	Clinical experts9

population of asymptomatic or mildly symptomatic adult men with progressive mHRPC who failed ADT and had not yet received cytotoxic chemotherapy (chemo-naive)	failed ADT and had not yet received cytotoxic chemotherapy, which is the proposed indication. Clinical experts in the UK confirmed that the PREVAIL population reflected that of the UK clinical practice.	
A naive comparison is the most suitable method to compare enzalutamide and abiraterone	As COU-AA-302 and PREVAIL had a similar setting, design and population, whereas the control arms (prednisone and placebo) were different, it was argued that an adjusted indirect comparison is not statistically appropriate. Therefore a naïve comparison was chosen as the most suitable method. Therefore, the survival curves from COU-AA-302 have been applied directly in the model.	Clinical experts9
OS with enzalutamide and with BSC is modelled according to the survival in PREVAIL trial adjusted to the UK treatment pathway (i.e. patients receive docetaxel as 2nd line treatment or move directly to palliative care)	The adjusted OS is most relevant for clinical practice, as it contains less impact of drugs not in the local treatment pathway	Clinical experts9
COU-AA-302 trial data do not need adjusting for switching	At the time of the 3rd interim analysis of the COU-AA-302 trial not many life extending post-study treatments were available. Also no patient level data or adjusted survival curves are available for the COU-AA-302 study.	Enzalutamide SPC1, abiraterone SPC4
Proportion of patients progressing to PP1 is equal for enzalutamide, abiraterone and BSC	As described in 7.3.1.3, the more mature data from the placebo arm of PREVAIL were used to inform the proportion of patients moving onto 2nd line treatment, regardless of treatment arm	Clinical experts9
Treatment discontinuation is the best proxy for disease progression	Oncologists in the UK confirmed that disease progression in prostate cancer in clinical practice is not a decision made using any single assessment measure alone (e.g. by radiographic or PSA progression alone) because of the advanced nature of disease in this patient population. In line with this, NICE has accepted this endpoint in previous HTA submissions[32]. Disease progression was based on the treatment discontinuation criteria in the trial.	Clinical experts9 Enzalutamide manufacturer submission[32]
Only grade ≥3 AE are taken into account.	Any incremental difference in Grade 1/2 AEs was not assumed to impact cost effectiveness results. This is in line with enzalutamide post-chemotherapy submission.	Enzalutamide manufacturer submission[32]
The effects of the included SRE's have a 1-month impact in terms of HRQL and costs.	No data on the duration of SREs was collected in PREVAIL. Based on data identified in the literature, a one month duration was considered reasonable. However, according to clinical experts this value may underestimate the real duration for certain SREs such as pathological bone fracture and spinal cord compression which in many cases can last for 3 or more months and lead to a lifetime paraplegia. Consequently, the impact of the duration of SREs was been assessed in a scenario.	Botteman 2010[115] Clinical experts9
SREs result in an additional decrement in utility over the decrement of progression	Both SREs and progression were associated with a significant decrease in utility. Available literature also indicates these events result in a decrease in HRQL.	Enzalutamide manufacturer submission[32]
SRE rates for enzalutamide and abiraterone are equal	As discussed in 7.3.1.7, no information on SREs in patients treated with abiraterone in the chemo-naïve setting was available. Therefore it was conservatively assumed that patients treated with abiraterone show	Assumption

	the same probability of experiencing a SRE as patients treated with enzalutamide.	
Approximation of OS and PFS curves assumed a parametric function	Not all patients have died, progressed, or discontinued treatment at the end of PREVAIL. Therefore, in line with NICE DSU guidance on survival modelling, the available survival data was fitted to parametric functions. A Weibull function was selected by clinical experts for OS, and Gamma for TTD.	Clinical experts9 NICE DSU guidance on survival modelling[105]
The model assumes enzalutamide is given to all patients in the PP2 health state	Although patients could in clinical practice receive either enzalutamide or abiraterone, for simplicity, the model assumes all patients receive enzalutamide. An alternative scenario with abiraterone given in the PP2 is explored.	Assumption
Treatment emergent periods to calculate AEs rates for enzalutamide and abiraterone are the same	As no information on treatment emergent period to calculate AEs rates for abiraterone was available, it was assumed to be the same as for enzalutamide.	Assumption
rPFS is assumed to represent TTD for abiraterone	As TTD has not been not reported in the COU-AA-302 study, rPFS was assumed to be equivalent to TTD	Assumption

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; HRQL: health related quality of life; mHRPC: metastatic hormone-relapsed prostate cancer; OS: overall survival; PFS: progression free survival; PSA: prostate specific antigen; SPC: summary of product characteristics; SRE: skeletal related event; TTD: time to treatment discontinuation; UK: United Kingdom.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The HRQL of patients with prostate cancer decreases as the disease progresses[116,117] and is worst in the last phase of life[118]. Decline in HRQL is partly due to the presence of bone metastases as documented in the study of Hechmati et al[119]. The authors compare patients with bone metastases to patients at high risk of bone metastases. HRQL in terms of EQ-5D and FACT-P was significantly worse for

patients with metastases. These outcomes are further supported by other studies[102,103].

A decline in HRQL for patients with bone metastases is partly due to the presence of debilitating SREs. Pain also accounts for the worse HRQL in mHRPC. In these patients pain is often a result of bone metastasis, and has a significant impact on the HRQL[118].

An additional cause of decline in HRQL for patients with mHRPC is treatment and its related toxicity. A study in German mHRPC patients found that patients on chemotherapy had worse HRQL than chemo-naïve patients and than patients no longer on chemotherapy[120]. Chemotherapy is associated with significant toxicity that negatively impacts the HRQL of patients. In these patients, chemotherapy is administered with corticosteroids to reduce toxicity however, corticosteroids are also associated with their own toxicity which in turn may also impact negatively on the patient's HRQL. Although treatment toxicity is associated with a decline in patient's HRQL, chemotherapy has demonstrated an overall positive impact on patient's HRQL. Docetaxel has a positive impact on pain progression which leads to a reduction in the use of opioids[121].

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As mentioned in section 7.4.1, HRQL decreases as the disease progresses[116,117,118]. In PREVAIL, patients were asymptomatic or mildly symptomatic at study entry. However, approximately 50% of patients in the placebo arm experienced pain progression as measured with the BPI during the study[53]. The proportion of patients with pain progression was higher in the placebo arm than the enzalutamide arm, irrespective of the BPI item used to measure pain. Time to pain progression as assessed with the worst pain severity, the average pain severity and the pain interference scores was also longer with enzalutamide than with placebo[53].

In PREVAIL, there was a marked and statistically significant deterioration in HRQL in all FACT-P scores (except for social well-being) versus baseline in the placebo arm at all timepoints[53].

The decline in HRQL in mHRPC is associated with further disease progression; therefore, delaying progression is also expected to have a substantial effect on HRQL. As indicated in section 7.4.3, progression has been shown to cause a significant decline in utility in the PREVAIL study. However, when compared with patients in the placebo arm, enzalutamide significantly delayed the decline in HRQL observed in the placebo arm of PREVAIL (section 6.5.3.3).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the

HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQL data were collected in the PREVAIL study through the EQ-5D 3 level questionnaire. EQ-5D data were collected in weeks 1, 13, 25 and then every 12 weeks up to progression. EQ-5D utility weights were calculated using the preference-based algorithm derived from the UK general population[122].

The mean baseline EQ-5D value of all PREVAIL subjects was 0.844 [95% CI: 0.836-0.852]. Although this may seem high, it should be taken into account that these patients are asymptomatic or mildly symptomatic and thus do not yet experience many problems related to the condition. This is lower than the median EQ-5D for men aged 65-74 of 0.92[123].

As HRQL was only collected for patients on treatment, it was not possible to calculate the disutility of treatment discontinuation from PREVAIL. Therefore, the utility values used in the model for progressed health states come from the literature (section 7.4.9).

Utility values per health state are summarised in Table B68.

As enzalutamide slows radiographic progression of the disease, it could also reduce clinical symptoms of progression, which may lead to better HRQL. To identify a possible difference in HRQL between enzalutamide and placebo within Stable Disease, a mixed-effects model for repeated measures (MMRM) analysis was performed. The outcome was change from baseline, and the predictors were baseline score, treatment, site, ECOG-PS at baseline, fatigue severity at baseline, pain at baseline, age, time (treated as a categorical variable), time by treatment arm interaction, and time by baseline value interaction.

As presented in Table B64, the least squares (LS) mean estimates for mean changes from baseline for enzalutamide versus placebo was estimated to be 0.022 (95% CI: 0.003 – 0.041, p=0.021), which means that in PREVAIL treatment with enzalutamide resulted in significantly higher HRQL compared to placebo. The on-treatment utility gain was added to the utility value for patients on enzalutamide in the Stable Disease health state.

Table B64 Change from baseline in EQ-5D for patients with stable disease

Statistics	ENZA	PLA	ENZA vs PLA
LS Mean (SE)	-0.042 (0.010)	-0.064 (0.012)	0.022 (0.009)
95% CI	(-0.061, -0.022)	(-0.087, -0.041)	(0.003, 0.041)
p-value	<.001	<.001	0.021

Abbreviations: CI: confidence interval; LS: least squares; SE: standard error.

The decrement of utility for patients experiencing an SRE was derived from PREVAIL EQ-5D data as follows:

- All patients included in PREVAIL who were alive and experienced an SRE of any type (pathologic bone fracture, spinal cord compression, and the need for radiotherapy or surgery to bone) were identified
- A linear mixed-effects model was used to model each patient's longitudinal trajectory of the collected EQ-5D utility values over time before the SRE
- The utility decrement was derived using the trajectory adjusted mean change, defined as the mean deviation of the post-event utility from the expected value based on all patients' pre-event trajectory.

The derived utility decrements for each type of SRE are displayed in Table B65.

The impact of any SRE was assumed to last for 1 month (range 0-90 days), which is equal to the assumption taken by Botteman et al[115]. However, as already mentioned (Table B63) clinical experts9 indicated that certain SREs, particular pathological fractures and spinal cord compression can last for much longer. The clinical experts who participated in the advisory board meetings related to this submission mentioned that on average, SREs may last for up to 7 months9. Therefore, duration of SRE was varied in SA using CI of 0-213 days.

Table B65 SRE disutilities based on PREVAIL

SRE	Mean	CI (days) / SE	Source
Spinal cord compression	-0.237	SE = 0.079	PREVAIL PRO analysis[53]
Pathological bone fracture	-0.201	SE = 0.080	PREVAIL PRO analysis[53]
Radiation to the bone	-0.056	SE = 0.021	PREVAIL PRO analysis[53]
Surgery to the bone	-0.056	SE = 0.021	PREVAIL PRO analysis[53]
Duration of disutility	30.42	CI: 0-213	Mean – Botteman 2011[115] CI: clinical experts9

Abbreviations: CI: confidence interval; SE: standard error; SRE: skeletal related event.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was conducted.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic literature review was carried out to identify utility studies in adults (over the age of 18) with either asymptomatic or symptomatic mHRPC[124]. The search strategy is detailed in section 10.12. Briefly, the strategy was constructed to identify the following concepts: (prostate cancer) AND (metastatic disease) AND (utilities).

The search strategy had a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The strategy excluded some publication types which are unlikely to yield relevant reports: news, comments, editorials, letters and case reports. The strategy also excluded animal studies. The searches were not limited by date range or language.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.

- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The studies presenting utilities in patients with mHRPC are summarised in Table B66.

Table B66 Studies measuring HRQL in mHRPC patients

Study	Country	Sample Size	Measurement Instrument	Perspective	High anchor of utility	Disease, treatment description	Utilities (Mean utility with standard error)
Bahl[125,126]	Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Finland, Hungary, India, Ireland, Italy, Luxembourg, Malaysia, Mexico, Philippines, Poland, Portugal, Romania, Singapore, Slovakia, Spain, Sweden, Taiwan, United Kingdom. No detail on whether patients in all countries completed EQ-5D, or for which time points.	108	EQ-5D	Patients	NR	mHRPC. All patients previously treated with docetaxel-containing regimen pre-trial, then received Cabazitaxel.	0.698 Baseline (i.e. no treatment) [N=100] 0.730 Cycle 2 [N=97] 0.765 Cycle 4 [N=74] 0.761 Cycle 6 [N=63] 0.781 Cycle 8 [N=37] 0.817 Cycle 10 [N=28] 0.695 30 days post treatment [N=62]
Diels[127]	Belgium, France, Germany, Netherlands, Sweden, the UK	602 (Belgium: N=45; France: N=94; Germany: N=272; Netherlands: N=89; Sweden: N=23; UK: N=79)	FACT-P mapped to EQ-5D	Patients	NR	mHRPC including chemo-naïve (39%), ongoing chemotherapy (37%) and post-chemotherapy (24%)	Belgium: observed: 62; OLS predicted: 0.66 France: observed: 0.62; OLS predicted: 0.61 Germany: observed: 0.64; predicted: 0.63 Netherlands:

Study	Country	Sample Size	Measurement Instrument	Perspective	High anchor of utility	Disease, treatment description	Utilities (Mean utility with standard error)
							observed: 0.75; predicted: 0.76 Sweden: observed: 0.78; predicted: 0.72 UK: observed: 0.69; predicted: 0.7
Fassler[128]	NA – systematic review	NR	NR	NR	NR	HRPC – hip fracture	0.03 [utility decrement]
Hechmati[119]	France, Germany, Italy, Spain, UK.	165 bone mHRPC, 36 high-risk of bone mHRPC	EQ-5D	Patients (clinicians also interviewed but implicitly their data is not used in this study)	NR	HRPC	0.59 Bone metastases HRPC patients 0.77 High-risk for developing bone metastases HRPC patients
James[129]	UK, France, Germany, USA	74	EQ-5D	Patients	NR	mHRPC. 81% had good ECOG performance (Score 0 or 1). Progressed during or after first line docetaxel.	0.63 (0.26)
Sandblom[118]	Sweden	1243	EQ-5D	Patients	NR	Patients with prostate cancer	0.770 (0.015
Skaltsa[130]	UK, France, Germany, Italy, Spain	236	EQ-5D	Patients	No problems	mHRPC. 94% had good ECOG performance. All had at least one previous chemotherapy. Progressed during or	0.688 (0.282)

Study	Country	Sample Size	Measurement Instrument	Perspective	High anchor of utility	Disease, treatment description	Utilities (Mean utility with standard error)
						after first line docetaxel.	
Spencer[131]	France, Germany, Italy, Spain, UK with country specific utility values derived from EQ-5D profiles based on value sets for 8 countries and the EU.	NR	EQ-5D	Patients	NR	mHRPC. 57% of patients were treated with chemotherapy at the time of assessment, 10% had prior chemotherapy, and 33% were chemotherapy naive. This is not country specific.	New Zealand (lowest reported country value) 0.59 Germany (highest reported country value) 0.76
Stopeck[132], Fizazi[133]	39 unnamed countries in trial. Unclear whether patients in all countries completed EQ-5D.	1904 in trial. Unknown how many completed EQ-5D	EQ-5D	Patients	NR	mHRPC. Patients had to have had documented failure of at least one hormone therapy. EQ-5D provided at baseline before treatment for bone metastasis. 14% had recent chemotherapy.	0.68
Winquist[134]	Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Finland, Hungary, India, Ireland, Italy, Luxembourg, Malaysia, Mexico,	55	EQ-5D	Patients	NR	mHRPC. 92.7% were ECOG 0 or 1, 87% had bone metastases. Treated with cabazitaxel.	0.713 Baseline (i.e. no treatment) 0.769 Cycle 4

Study	Country	Sample Size	Measurement Instrument	Perspective	High anchor of utility	Disease, treatment description	Utilities (Mean utility with standard error)
	Philippines, Poland, Portugal, Romania, Singapore, Slovakia, Spain, Sweden, Taiwan, United Kingdom. No detail on whether patients in all countries completed EQ-5D, or for which time points.						
Wolff[120]	Germany	101 (33 no chemotherapy, 37 past chemotherapy, 31 ongoing chemotherapy) [interim results]	EQ-5D	Patients	NR	mHRPC	0.72 (0.30) [SD] all patients 0.81 (0.27) [SD] no previous chemotherapy 0.66 (0.30) [SD] past chemotherapy 0.64 (0.31) [SD] ongoing chemotherapy
Wu[135], Sullivan[136]	Australia, Canada, France, Germany, Italy, UK, USA	280 (UK 29)	EQ-5D	Patients	NR	mHRPC. TURP 14%, External beam therapy 53%, Bone seeking radioscope 8%, Other 25%	0.635 (0.309) [SD] 0.715 (UK) [SD not provided)

Source: Systematic literature review on health utilities[124]
Abbreviations: NA = Not applicable, NR = Not reported, OLS: ordinary least squares, SD = Standard Deviation.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The baseline utility in the model (Stable Disease) has been derived from the EQ-5D data collected in the PREVAIL study. As detailed in Table B21, the number of patients providing EQ-5D data in PREVAIL was large (EQ-5D at baseline: enzalutamide: N=856/872; placebo: N=825/845; FACT-P at baseline: enzalutamide: N=865/872; placebo: N=834/845) with approximately 50% of them being European patients with asymptomatic or mildly symptomatic mHRPC. Accordingly, the utility derived from PREVAIL was considered the most appropriate utility for the stable disease health state of the economic model.

The value derived in PREVAIL is similar to that observed in Wolff et al[120] for chemo-naïve mHRPC patients. The authors indicate a utility of 0.81. In contrast, these values are higher than those published in other studies for mHRPC patients. This is likely to be the result of the differences in the cancer stage across studies. HRQL declines as the disease progresses. The utility values reported by Bahl et al[125,126] (0.698), James[129] (0.63), Skaltsa[130] (0.688), Spencer[131] (0.59 – 0.76), Winquist[134] (0.713), and Wolff[120] (0.72) are indeed lower. In these studies, patients were either being treated with chemotherapy or had already progressed after chemotherapy. These patients thus are at a more progressed stage than patients in PREVAIL.

In the model the utilities used for the post-progression treatment states have been derived from the utility weights reported by Wolff et al[120] (0.66±0.30 for patients who have had chemotherapy in the past and 0.64±0.31 for patients on chemotherapy) and Diels et al[127] (0.69 for all patients with mHRPC in the UK). The modelled utilities for PP1 and PP2 are a weighted mean of these utility weights; 0.658 and 0.612, respectively. In addition, the utility weight for palliative care is the utility reported in Sandblom et al (utility: 0.5).

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

AEs are likely to have a negative impact on the HRQL of patients; therefore, it is important to account for the associated disutility. In the absence of disutility data from PREVAIL (aside from SRE values), the disutilities of experiencing an AE were sourced from the published literature. When disutilities estimates were identified in different sources, an average was taken and this value used to inform the model. The duration of each AE considered were based on values reported in the abiraterone post-chemo ERG report[137]. The disutilities and durations used in the model are reported in Table B67. As most AEs have a duration <2 weeks, whereas QoL was measured every 12 weeks, it is unlikely that the impact of AEs was captured in the on treatment benefit. However a scenario analysis to exclude any potential double counting was conducted and the results are presented in section 7.7.10.

Table B67 Disutility and duration of adverse events

AE	Disutility	SE	Justification / Source	Duration (days)
Anaemia	-0.12	0.047	Swinburn (2010)[138]	7-14
Arthralgia	-0.07	0.012	Doyle (2008)[139]	7-14
Back pain	-0.07	0.012	Doyle (2008)[139]	7-14
Bone pain	-0.07	0.012	Doyle (2008)[139]	7-14
Deterioration in general physical health	-0.13	0.030	Assumed equal to fatigue: Lloyd (2006)[140], Nafees (2008)[141], Swinburn (2010)[138]	91.25
Dyspnoea	-0.05	0.012	Doyle (2008)[139]	7-14
Fatigue	-0.13	0.030	Lloyd (2006)[140], Nafees (2008)[141], Swinburn (2010)[138]	91.25
Febrile neutropenia	-0.12	0.016	Lloyd (2006)[140] and Nafees (2008)[141]	7-14
Hypertension	-0.15	0.049	Swinburn (2010)[138]	7-14
Hypokalaemia	0.00	0.000	No (dis-)utilities reported, assumed to have no detrimental impact on HRQL	7-14
Neutropenia	-0.09	0.015	Nafees (2008)[141]	7-14
Oedema Peripheral/Fluid retention	0.00	0.000	No (dis-)utilities reported, assumed to have no detrimental impact on HRQL	7-14

Abbreviations: AE: adverse events; SE: standard error.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utility values per health state are summarised in Table B69.

Table B68 Utility values per health state

Health state	Value	95% CI	Source
Stable Disease	0.844	0.836-0.852	PREVAIL
PP1*	0.658	0.574-0.741	Wolff 2012[120] and Diels 2014[127]
PP2*	0.612	0.304-0.920	Wolff 2012[120] and Diels 2014[127]
Palliative care	0.5	0.344-0.656	Sandblom 2004[118]
Death	0	N/A	Definition

Abbreviations: CI: confidence interval; N/A: not applicable; PP1: post-progression 1; PP2: post-progression 2.
*The utility weights correspond to the weighted mean.

As no data for an on treatment utility gain in patients treated with abiraterone vs placebo were available, an on treatment utility gain equal to that experienced by patients treated with enzalutamide was assumed (section 7.4.3).

In line with the post-chemotherapy NICE appraisal for enzalutamide[32], an on treatment utility gain for patients treated with enzalutamide after docetaxel has been applied in the model. This on treatment utility gain (0.04, SE: 0.004) was based on the committee preferred scenario[99].

Table B69 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	CI / SE	Reference in submission	Justification
Stable disease	0.844	SE: 0.0039	7.4.3	The baseline utility (EQ-5D) values in PREVAIL represent patients in Stable Disease.
PP1	0.658	SE: 0.0065	7.4.9	Literature value
PP2	0.612	SE: 0.0242	7.4.9	Literature value
Palliative	0.500	SE: 0.08	7.4.9	Literature value
On treatment benefit for enzalutamide	0.022	95% CI: [0.003; 0.041]	7.4.3	Enzalutamide showed a significant utility gain over placebo in PREVAIL
On treatment benefit for abiraterone	0.022	95% CI: [0.003; 0.041]	7.4.3	Assumed equal to enzalutamide
On treatment benefit for enzalutamide given after docetaxel	0.04	95% CI: [0.032; 0.048]	7.4.3	Enzalutamide and abiraterone showed a significant utility gain over placebo in AFFIRM and COU-AA-301 respectively
SRE disutilities			7.4.3	
Spinal cord compression	-0.237	SE = 0.079		SREs in PREVAIL were associated with a significant decline in utility.
Pathological bone fracture	-0.201	SE = 0.080		
Radiation to the bone	-0.056	SE = 0.021		
Surgery to the bone	-0.056	SE = 0.021		
Duration of disutility (days)	30.42	0-213		
AE disutilities	See Table B67		7.4.8	Literature values were used as impact of individual AEs could not be measured in PREVAIL due to frequency of HRQL measurements

Abbreviations: AE: adverse event; CI: confidence interval; SE: standard error; SRE: skeletal related event

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[‡‡]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The health utility values for the health economic model and the method to derive the on treatment utility gain, and disutilities for progression and SREs were validated during an Advisory Board meeting9. Experts who participated in the Advisory Board meeting agreed that the patient population of interest will experience a gradual decline in HRQL.

The Advisory Board meeting is described in section 7.3.5. Briefly, 7 UK experts participated in this NICE-specific Advisory Board. Of these, 6 were clinicians and the last attendee a health economist. All experts participating in the meeting declared no potential conflict of interest9.

[‡‡] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

During the meeting, the different health utility values and their applicability to the decision problem was discussed. The source of the different utility values was provided to the attendees9.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

A patient in Stable Disease experiences a constant utility, consisting of the Stable Disease utility value and an on treatment utility benefit for patients treated with enzalutamide or abiraterone. The utility in Stable Disease may be decreased for a number of days due to the occurrence of AEs and SREs.

Once patients progress to the PP1 treatment state they no longer experience any on-treatment utility benefit, except for the on-treatment utility benefit in the PP2 health state for the BSC arm where patients get enzalutamide after docetaxel. Furthermore their utilities in the PP1, PP2 and palliative care treatment states are decreased as a result of progression. The utilities in these health states are constant, but may be decreased for a number of days due to the occurrence of AEs and for a duration of 1 month due to the occurrence of SREs.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

None of the health effects identified in the literature or in PREVAIL have been excluded from the analysis.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients enter the model in the Stable Disease health state; the baseline HRQL is the utility of this health state and originates from the PREVAIL study. All HRQL events (i.e., AEs, treatment gain, progression) were taken from this baseline.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed constant over time in each health state. This is in line with the outcomes of PREVAIL where no clinically meaningful decrease was observed for the FACT-P or EQ-5D in the enzalutamide arm (see section 6.5.3.3).

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values have not been amended. The values used in the model for the post-progression states were derived from the values provided by Wolff et al[120], Diels et al[127] and Sandblom et al[118] and correspond to the weighted mean.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The only tariff that is relevant to mHRPC patients in the chemo-naïve setting is the chemotherapy tariff. This tariff is relevant to all patients receiving chemotherapy in the model.

The clinical management of mHRPC patients is currently costed using NHS reference costs for scheduled monitoring, chemotherapy administration, management of AEs and SREs, and terminal treatment costs[142].

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The chemotherapy tariff only applies to patients receiving chemotherapy. The following costs sources are also used in the economic model:

- British National Formulary (BNF) 68, September 2014[143], and Electronic Market Information Tool (eMit)[144] for drug costs.
- NHS reference costs 2012-2013 for diagnostic imaging and tests, palliative care, and AE and SRE management costs[142]
- Unit costs for Health and Social Care 2013 for outpatient visits and home care[145].

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic literature search of health resource utilisation has been conducted[146]. The methodology used, including selection criteria of studies is detailed in Appendix 13, section 10.13.

Overall, 13 studies were selected for review. Table B70 provides a summary of the main characteristics and the treatments included in these studies.

The search addressed three different types of resource utilisation: treatment costs and monitoring, hospital utilisation and GP visits.

<u>Treatment costs and monitoring</u>

In terms of treatment use, in the Morote et al study conducted in Spain, ongoing hormone therapy costs in metastatic patients were reported to be €946 in the first year, €948 in the second year and €948 in the third year[154]. Chemotherapy costs in

metastatic patients were €1,892 in the first year, €9,485 in the second year and € 9,144 in the third year. Analgesic costs in metastatic patients were €597 in the first year, €915 in the second year and €1,031 in the third year. Costs included drug, adverse events management and pre-medication costs.

Clinicians in Argentina reported that the most common treatment order at castration resistance was docetaxel, mitoxantrone and then abiraterone[155]. Dass et al report use of chemotherapy across the UK, Belgium, France, Germany, Sweden and Netherlands. In these countries, docetaxel had been used by 82.0% of patients who were receiving or had received chemotherapy[151].

Regarding docetaxel use, the NICE Prostate Cancer guidelines for England and Wales recommend docetaxel if Karnofsky performance is greater than 60%, for up to ten cycles with no repeat cycles recommended[31]. The Scottish Medicines Consortium (SMC) in 2011 also recommended 10 cycles in Scotland, intravenously at 75mg/m^2 over sixty minutes[156]. Collins reported 75mg/m^2, given weekly or three-weekly, for 7.3 cycles in the UK[150]. Each cycle is assumed to include one outpatient appointment at a cost of £177; follow-up costs are reported in Collins for between 6 and 26 months at four monthly intervals ranging from £718.40 (for 10-14 months) to £7,616.34 (for 18-22 months); for greater than or equal to 26 months (£4,827.96); and for terminal care (£3,527.95)[150]. The number of outpatient appointments in Collins et al is slightly higher than that estimated in the enzalutamide model where 1 appointment (either with consultant or nurse) is estimated every 4 weeks during the first 3 months and every 8 weeks thereafter for patients treated with enzalutamide and every 6 weeks for patients on BSC.

For Spain, Marquez-Fernandez et al reported docetaxel use for 7 cycles at 40mg/m^2 and then reduced to 30mg/m^2 due to adverse reactions[153]. Ansari reported that, of 42 patients who received docetaxel as first-line therapy, ten had it as re-treatment and three as second re-treatment in the UK[147]. Cycles were three-weekly with a median of seven cycles for first-line treatment and six for re-treatment[147].

Regarding mitoxantrone, Janssen reported use of 24mg of mitoxantrone following progression after other chemotherapeutic drugs at a cost of £248.45 per cycle in the UK in 2012[152]. Collins reported 12mg/m^2 dosage for 5.9 cycles in the UK in 2007[150]. With each cycle assumed to be one outpatient appointment at a cost of £177, follow-up costs are reported for between 6 and 26 months at four monthly intervals ranging from £1,753.84 (for 10-14 months) to £73,286.83 (for 18-22 months); for greater than or equal to 26 months (£12,679.52); and for terminal care (£3,942.16) in the UK in 2007. Five mg of prednisone, 140mg of estramustine, and 1mg of warfarin, clodronate, bisphosphonates and granulocyte colony-stimulating factor (G-CSF) were used concomitantly[150]. The SMC recommended ten cycles for Scottish patients, intravenously at 12mg/m^2 dosage over 15 to 30 minutes, if docetaxel is not tolerated[156].

Three studies described the use of abiraterone on progression after docetaxel[152,153,158] and one the use of enzalutamide[157].

Two studies reported cabazitaxel usage. Vitale reported use as third-line treatment after docetaxel followed by abiraterone[158]. According to Vitale et al, cabazitaxel is used for six cycles in Brazil in 2013[158]. Bracarda reported dosage as 25mg/m^2; 50.6% of patients completed six cycles, once every three weeks in Italy in 2013[149]. Concomitant medication is reported to be prednisone (daily), antihistamine,

corticosteroid and ranitidine. Patients at high risk of febrile neutropenia had G-CSF[149].

Bonetta reported 600mg daily dosage of ketoconazole, which is used to prolong the time to PSA progression after standard hormonal therapy in Italy in 2011[148].

Janssen estimated the number of outpatient visits for patients on mitoxantrone as one visit every three weeks whilst on treatment and one visit every six weeks whilst off treatment in the UK in 2012[152]. Patients on abiraterone were estimated to have one visit every two weeks in the first three months and one visit every month thereafter[152].

In COU-AA-302, health resource utilisation was collected. Janssen estimated the cost associated with unexpected health resource utilisation in the UK patient subset[35]. Resource use collected during the COU-AA-302 trial were classified into five categories: 1) hospitalisations (note: length of stay data were not collected), 2) GP visits, 3) nurse visits, 4) site investigator visits (assumed to be urologist visits), and 5) other (free text such as emergency department, computed tomography scan). The total cost per patient was higher in the abiraterone arm, but it was not statistically significantly different from the cost per patient in the placebo arm[35]. The average cost per patient for unscheduled resource utilisation was:

- £1,410.11 for abiraterone
- £647.29 for placebo.

The cost of outpatient visits was the major driver for the total MRU cost. Overall, the results indicated that the unplanned MRU cost was independent of treatment arm but dependent on the treatment duration. Therefore, in the model, a weekly unplanned MRU cost (£21.57 per week) was applied to both treatment arms for the duration patients stayed on treatment[35].

The 2014 NICE Prostate Cancer guidelines recommend a MRI scan in England and Wales only if there are extensive metastases on the spine[31]. Janssen estimated one MRI scan, one CT scan, one ECG, one ultrasound and one bone scan across all treatments in 5% of patients every six weeks in the UK in 2012[152]. Estimates were also given for full blood count testing, liver/kidney function tests and PSA lab tests. Collins reported the cost of blood tests as £14 for docetaxel patients and £12 for mitoxantrone patients in the UK in 2007[150].

<u>Hospitalisations</u>

Data for utilisation of hospital resources were sparsely reported and there were no data reported for bed days, staffing or nurse visits.

Dass reported mean hospitalisation by rate and days for the UK, Belgium, France, Germany, Sweden and Netherlands in 2012, chemotherapy naïve patients (23.5%; 5.7 days), patients with prior chemotherapy (43.7%; 6.1 days) and patients currently receiving chemotherapy (43.5%; 6.8 days)[151].

Dass reported the following rates in 2012 in the UK, Belgium, France, Germany, Sweden and Netherlands[151]:

- Rates of Accident and Emergency visits for chemotherapy naïve patients as 7.4%, for patients with prior chemotherapy as 9.9% and for patients currently receiving chemotherapy as 14.5%

- Rates of surgery for chemotherapy naïve patients as 5.9%, for patients with prior chemotherapy as 11.3% and for patients currently receiving chemotherapy as 12.9%
- Rates of radiotherapy for chemotherapy naïve patients as 19.1%, for patients with prior chemotherapy as 28.7% and for patients currently receiving chemotherapy as 14.5%.

GP visits

The number of GP visits was not reported in any of the identified studies. Janssen estimated that during the last three months of life, a patient in the UK would receive home care by a nurse for one hour, twice a day for fourteen days a month[152].

Table B70 Summary of the main characteristics of the studies providing health resource utilisation by mHRPC patients

Study	Country	Year of publication	Number of mHRPC respondents	Date / time point information collected	Type and number of treatments
Ansari[147]	UK	2008	42	During chemotherapy and through to maximum of 36 months.	Docetaxel. 10/42 (23.8%) of patients with first line docetaxel, received second treatment and 3/42 (7.1%) had third treatment. Three weekly regimen. Median number of cycles was 7 in first line and 6 in second line.
Bonetta[148]	Italy	2011	NR	During treatment	Ketoconazole 600mg; daily treatment but duration was not reported.
Bracarda[149]	Italy	2013	218	During treatment	Cabazitaxel 25mg/m^2 once every three weeks. 50.6% completed the six cycles.
Collins[150]	UK	2007	N/A	During treatment for mHRPC.	Docetaxel 75mg/m^2; 3 weekly: 7.3 cycles; weekly: 7.3 cycles. Mitoxantrone 12mg/m^2; 5.9 cycles.
Dass[151]	UK, Belgium, France, Germany, Sweden, Netherlands	2012	212	During treatment for mHRPC.	Docetaxel in 82.0% of patients receiving or who had received chemotherapy. Number not reported.
Janssen post-chemo ABI[152]	UK	2012	N/A	Following progression after previous chemotherapy.	Abiraterone acetate 1000mg daily for three weeks, prednisolone 10mg, mitoxantrone 24mg once every three week.
Marquez-Fernandez [153]	Spain	2013	1	Initial chemotherapy and subsequent treatment on disease progression.	Docetaxel 40mg/m^2. Reduced to 30mg/m^2 due to adverse reaction during treatment. On progression; weekly for 7 cycles. Abiraterone 1,000mg/24h; appears to have been administered once.
Morote[154]	Spain	2013	NR	HRPC with and without bone metastases.	Hormone therapy, chemotherapy; number not reported.

Study	Country	Year of publication	Number of mHRPC respondents	Date / time point information collected	Type and number of treatments
NICE CG175[31]	UK	2014	N/A	During treatment for mHRPC.	Docetaxel if Karnofsky performance is >60%; up to 10 cycles. No repeat cycles recommended. Corticosteroid (e.g. dexamethasone 0.5mg daily) as third line hormonal therapy.
Peirano[155]	Argentina	2013	N/A	At castration resistance.	Lists most common treatment order given by clinicians: docetaxel, mitoxantrone, abiraterone; number not reported.
Cabazitaxel SMC 2011[156]	Scotland	2011	N/A	Progression following docetaxel.	Docetaxel 75mg/m^2 intravenous over 60 minutes; 10 treatments. If docetaxel is not tolerated mitoxantrone 12mg/m^2 intravenous over 15 to 30 minutes; 10 treatments.
Enzalutamide SMC 2013[157]	Scotland	2013	N/A	Progression following docetaxel.	Enzalutamide 160mg orally once daily; continuously.
Vitale[158]	Brazil	2013	NR	Progression following docetaxel.	Abiraterone acetate; 8 cycles. Cabazitaxel; 6 cycles.

Source: Systematic literature review for health resource utilisation[146]
Abbreviations: mHRPC, metastatic hormone-relapsed prostate cancer; N/A, not applicable; NR, not reported.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[§§]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Using the methodology described in section 7.3.5, the values for resource utilisation were discussed with clinical experts. In particular the resource utilisation for regular monitoring as reported in the enzalutamide[32] and abiraterone[35] manufacturer submission for the post-chemotherapy and chemo-naïve settings, respectively was discussed with the experts, and modified according to the consensus at the advisory board9. In addition, the included cost categories, concomitant medication, terminal treatment costs and the exclusion of additional hospitalisation costs were validated at the advisory board conducted to discuss the economic model9.

Health resource utilisation in the UK for the population of relevance was discussed in the Advisory Board meeting described in section 7.3.5. As already mentioned, 7 UK

[§§] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

experts participated in this meeting of which 6 were clinicians from different large England hospitals.

During the meeting, the health resource utilisation proposed in the model was discussed in detail 9.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Technology costs

The list price of enzalutamide is £2,734.67 for each 28 day pack (112 tablets of 40 mg). Astellas has agreed a PAS with the Department of Health, but this is not included in this revised submission, at the request of NICE. The PAS consists of a [redacted] discount, resulting in a price per pack of enzalutamide of [redacted] and a price per day of [redacted]

Abiraterone is available with a list price of £2,930 for each 30 day pack (120 tablets of 250 mg).

Monitoring

The monitoring requirements and frequency was based on the post-chemotherapy enzalutamide STA (Table 61 in the manufacturer submission[32]), and modified based on the experience of UK clinical experts (Table B71). According to UK clinical experts actively treating patients with mHRPC9, it was likely that monitoring would be alternated between a clinical oncologist and a nurse specialist; therefore, the model assumes half of all monitoring is performed by a clinical oncologist and half by a nurse specialist. As enzalutamide does not require the additional monitoring required for abiraterone4. the monitoring frequency was estimated at once every four weeks in the first three months, and once every 8 weeks thereafter. Unit costs for routine monitoring are shown in Table B72. The monitoring frequency for enzalutamide given after docetaxel is assumed to be in line with the monitoring frequencies for enzalutamide after 3 months of treatment in post-chemotherapy submission to NICE[32]. For a scenario where abiraterone is given after docetaxel, a similar approach was taken.

Table B71 Medical resource utilisation for monitoring of mHRPC patients on treatment

Resource	ENZA						BSC	
	First 3 months		Months 4+		Post-docetaxel			
	Frequency (every X weeks	% of pts	Frequency (every X weeks	% of pts	Frequency (every X weeks	% of pts	Frequency (every X weeks	% of pts
Outpatient visit consultant	4	50%	8	50%	8	100%	6	50%
Outpatient visit nurse	4	50%	8	50%	8	0%	6	50%
CT scan*	27	100%	27	100%	8	5%	7	100%
Radiographic/MRI scan	0	0%	0	0%	8	5%	0	0%
ECG	0	0%	0	0%	8	5%	0	0%
Ultrasound	0	0%	0	0%	8	5%	0	0%
Bone scan	12	20%	12	20%	8	5%	12	20%
Full blood count	4	100%	8	100%	8	100%	6	100%
Liver function test	4	50%	8	50%	8	100%	6	100%
Kidney function test	4	100%	8	100%	8	100%	6	100%
PSA	4	100%	8	100%	8	100%	6	100%
Cost (£) per week		**£34.66**		**£20.91**		**£24.82**		**£36.47**
Resource	**ABI**						**Docetaxel**	
	First 3 months		**Months 4+**		**Post-docetaxel**			
	Frequency (every X weeks	**% of pts**	**Frequency (every X weeks**	**% of pts**	**Frequency (every X weeks**	**% of pts**	**Frequency (every X weeks**	**% of pts**
Outpatient visit consultant	2	50%	4	50%	4	100%	3	100%
Outpatient visit nurse	2	50%	4	50%	4	0%	0	0%
CT scan*	22	100%	22	100%	8	5%	10	100%
Radiographic/MRI scan	0	0%	0	0%	8	5%	12	10%
ECG	0	0%	0	0%	8	5%	6	5%
Ultrasound	0	0%	0	0%	8	5%	6	5%
Bone scan	12	20%	12	20%	8	5%	12	20%
Full blood count	2	100%	4	100%	8	100%	1	100%
Liver function test	2	100%	4	100%	4	100%	3	100%
Kidney function test	2	100%	4	100%	4	100%	3	100%
PSA	2	100%	4	100%	8	100%	3	100%
Cost (£) per week		**£64.55**		**£36.26**		**£44.48**		**£73.87**

Abbreviations: BSC: best supportive care; CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; PSA: prostate specific antigen

*According to clinical experts9, 3 scans assumed during the course of treatment

Table B72 Unit costs for routine monitoring

Resource	Cost (£)	Code	Source
Outpatient visit consultant	£139.00	section 15.5	PSSRU 2013
Outpatient visit nurse	£42.00	section 10.4	PSSRU 2013
CT scan*	£106.45	DIAGIMOP RA10Z medical oncology	NHS Reference Costs 2012-2013
Radiographic/MRI scan	£241.85	DIAGIMOP RA03Z medical oncology	NHS Reference Costs 2012-2013
ECG	£140.16	OPROC EA47Z Clinical Oncology (Previously Radiotherapy)	NHS Reference Costs 2012-2013
Ultrasound	£62.37	DIAGIMOP RA23Z medical oncology	NHS Reference Costs 2012-2013
Bone scan	£192.90	DIAGIMOP RA36Z medical oncology	NHS Reference Costs 2012-2013
Full blood count	£3.01	DAPS DAPS05	NHS Reference Costs 2012-2013
Liver function test	£6.23	DAPS DAPS04	NHS reference costs 2012-2013. 5 tests required as reported in abiraterone manufacturer submission (TA259)
Kidney function test	£12.46	DAPS DAPS04	NHS reference costs 2012-2013. Assumed 10 tests, similar to abiraterone manufacturer submission (TA259)
PSA	£1.25	DAPS DAPS04	NHS Reference Costs 2012-2013

Source: PSSRU 2013[145]; NHS Reference Costs 2012-2013[142]
Abbreviations: CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; NHS: National Health Service; PSA: prostate specific antigen; PSSRU: Personal Social Services Research Unit.

Concomitant medication

Concomitant medication was based on the PREVAIL trial. In the health economic model, six concomitant medications have been included: anti-histamines, H2-antagonists, anti-emetic drugs, corticosteroids, G-CSFs and bisphosphonates (Table B73). Apart from the need for all abiraterone patients to receive prednisolone, concomitant medication use in the abiraterone arm was assumed equal to concomitant use in the enzalutamide arm (as per PREVAIL). However, given that incidence of SREs may be higher in patients treated with abiraterone than in patients treated with enzalutamide, the assumption of equal use of bisphosphonates can be considered as conservative. Dosing was taken from the British National Formulary (BNF 68)[143] and costs were taken from eMit[144] and BNF 68[143] (Table B74). As no concomitant medication use for patients on docetaxel was reported in TAX327 trial[109], it was assumed to be the same as for cabazitaxel[42].

Table B73 Use of concomitant medications

Medication	% requiring concomitant medication			
	ENZA	BSC	ABI	Docetaxel
Antihistamine	0%	0%	0%	100%
H2-antagonist	42%	38%	42%	100%
Anti-emetic	8%	8%	8%	100%
Corticosteroid	27%	30%	100%	100%
G-CSF	0%	0%	0%	25%
Bisphosphonates	35%	35%	35%	47%
Cost per 1 week (£)	6.86	6.93	7.15	71.65

Abbreviations: ABI: abiraterone; BSC: best supportive care; G-CSF: Granulocyte colony-stimulating factor; ENZA: enzalutamide

Table B74 Unit costs associated with concomitant medication

Resource	Cost per mg (£)	Dose (mg) per (1 week) cycle	Cost (£)/Cycle	Source
Antihistamine (chlorphenamine) 4mg every 4-6 hours, assumed for 5 days	0.002	40	0.08	eMit
H2-antagonist (ranitidine) 150mg BD, assumed for 5 days	0.0001	500	0.03	eMit
Anti-emetic (ondansetrone) 4 mg every 12 hours for up to 5 days; max of 32mg/day	0.01	27	0.39	eMit
Corticosteroid (prednisolone) twice daily oral 5 mg	0.01	70	0.40	eMit
G-CSF (filgrastim) 500,000 units/kg daily for up to 14 days	0.18/mcg	300 mcg	247	BNF68
Bisphosphonates (zolendronic) 4mg infusion every 6 weeks	14.43	1.3	19	eMit

Abbreviations: BD: twice daily; BNF: British National Formulary; G-CSF: granulocyte colony-stimulating factor; mg: milligram; mcg: microgram

A summary of the total treatment costs is shown in Table B75.

Table B75 Costs (£) per 1 week cycle in stable disease (PP1 for docetaxel)

Items	ENZA (£)	BSC (£)	ABI (£)	Docetaxel (£)
Technology cost per 1 week cycle	684	0	684	15
Administration cost	0	0	0	101
Monitoring cost (*Table B71)*	35* 21** 25***	36	65* 36** 45***	74
Concomitant medication (Table B73)	7	7	7	72
Total	719*705**709***	43	749&720**729***	262

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; * First three months; ** Subsequent months, *** Post-docetaxel

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

In addition to the treatment specific costs mentioned in section 7.5.5, the model includes costs for routine monitoring and medication in the PP1, PP2 and palliative care treatment states, and costs for the terminal phase of life.

Medications and monitoring in PP1 treatment state

According to the modelled treatment pathway (Table B45), for all treatment arms medication and monitoring costs in the PP1 treatment state consist of docetaxel costs and associated administration, monitoring and concomitant medication costs (Table B75).

Medications and monitoring in PP2 treatment *state*

PP2 treatment state is only applicable for the BSC arm where patients can receive an active treatment after progression on docetaxel. Although patients could in clinical practice receive either enzalutamide or abiraterone, for simplicity, the model assumes all patients receive enzalutamide (Table B45). As the cost of abiraterone including PAS is assumed to be the same as the cost of enzalutamide, this is not expected to influence results. Medication and monitoring costs in the PP2 treatment state consist of enzalutamide costs and associated monitoring and concomitant medication costs (Table B75). The monitoring required for patients receiving post-docetaxel enzalutamide was assumed to be in line with enzalutamide post-chemotherapy submission (Table B71).

Medications and monitoring in palliative care treatment *state*

Cost of medications and monitoring in the palliative care treatment state (£103.82/ 1 week cycle) was estimated based on Guest 2005[159] by dividing mean NHS costs at 2000/2001 prices of palliative prostate cancer care resource use per patient adapted to 2013 prices using consumer price index[160] by duration of palliative care (Guest 2005[159]).

Terminal treatment costs

As resource use and associated costs usually show a peak in the months immediately prior to death for patients with prostate cancer[161], a terminal care cost for a patient's last months has been incorporated in to the model. Following the estimates in the abiraterone submission[35], patients were assumed to receive home care by a nurse twice per day (assumed once during the day and once in the evening), for 14 days each month during the last 3 months of life. Fifty percent of patients typically die in a hospital (palliative care unit) and 50% die in a hospice centre. The duration of stay in each of these locations was assumed to be 14 days. Costs for a one hour home care visit in both a day and evening settings (averages to £23.50 per hour) were obtained from the PSSRU 2013[145]. Daily cost of both a

hospice centre and a palliative care unit of a hospital was £116, based on the NHS Reference costs 2012-2013[142]. This results in a terminal treatment cost of £3,598 per patient, which is applied in the model as a transition cost to the death state.

Table B76 List of health states and associated costs in the economic model

Health states	Items	Value (£)	Reference in submission
Stable Disease	All costs are treatment specific	-	Section 7.5.5
PP1 (£/cycle)	Medication	15	Section 7.5.5 Table B75
	Administration	101	
	Monitoring	74	
	Concomitant medication	72	
PP2	Medication	684	Section 7.5.5 Table B75
	Monitoring	35* 21**	
	Concomitant medication	7	
Palliative care	Medication	6.93	Section 7.5.5 Guest 2005[159]
	Monitoring	104	
Death (£, transition cost to the death state)	Terminal treatment	£3,598	PSSRU 2013[145] NHS Reference costs 2012-2013[142]

Abbreviations: PP1: post-progression 1; PP2: post-progression 2; PSSRU: * First three months; ** Subsequent months; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

Hospitalisations

No costs for hospitalisations were included in the base case. UK clinical experts confirmed that all hospitalisations would have been captured by AEs, SREs and terminal treatment costs.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Costs of AEs included in the model were derived from NHS reference costs 2012-2013[142] and NICE ERG report of post-chemo abiraterone[43].

Table B77 List of adverse events and summary of costs included in the economic model

AE	Cost (£)	Lower quartile cost (£)	Upper quartile cost (£)	Reference
Anaemia	1,779	1,301	2,113	NHS reference costs 2012-2013; NEI_L: Weighted average of SA04G, SA04H, SA04J, SA04K, SA04L
Arthralgia	176	136	244	Costs assumed to be equal to pain: NHS Reference Costs 2012-2013; NCL: WF02B; service code: 191 (Pain management, Multiprofessional Non-Admitted Non Face to Face Attendance, First)
Back pain	467	305	539	NHS Reference Costs 2012-2013; NEI_S: Weighted average of HC32D, HC32E, HC32F
Bone pain	606	369	704	NHS Reference Costs 2012-2013; NEI_S: Weighted average of HD40D, HD40E, HD40F
Deterioration in general physical health	12	9	15	Costs are not available in NHS reference costs 2012-2013; assumed to be equal to fatigue: NICE ERG report abiraterone (post-chemo), table 24, p. 64. IQR assumed ±25%
Dyspnoea	0	-	-	NICE ERG report abiraterone (post-chemo), table 24, p. 64. IQR assumed ±25%
Fatigue	12	9	15	NICE ERG report abiraterone (post-chemo), table 24, p. 64. IQR assumed ±25%
Febrile neutropenia	4,519	2,876	5,633	NHS reference costs 2012-2013; NEI_L: Weighted average of PA45Z
Hypertension	432	299	492	NHS reference costs 2012-2013; NEI_S: Weighted average of EB04Z
Hypokalaemia	348	98	435	NHS reference costs 2012-2013; HCD: XD26Z (Outpatients; Intravenous Nutrition, Band 1). The upper quartile cost is assumed to be +25% of mean as upper quartile in the NHS reference costs 2012-2013 is lower than the mean.
Neutropenia	161	81	246	NHS reference costs 2012-2013; HCD: XD25Z (Admitted Patient Care)
Oedema Peripheral/Fluid retention	914	686	1,143	NICE ERG report abiraterone (post-chemo), table 24, p. 64

Abbreviations: ERG: evidence review group; NHS: National Health Service; NICE: National Institute for Health and Care Excellence

Costs for SREs were included in the health economic model. The costing was derived from Botteman 2011[115], and recalculated using the 2012-2013 NHS Reference costs[142].

Table B78 Costs of SREs included in the economic model

SRE	Cost (£)	Lower quartile cost (£)	Upper quartile cost (£)	Reference
Spinal cord compression	4,688	2,719	6,234	NHS reference costs 2012-2013; NEI_L: Weighted average of HC28D
Pathological bone fracture	5,351	4,459	6,243	Average of HRG code HD39C, HD39B, HD39A weighted by the number of treatment in each HRG. Plus for patients with non-vertebral fractures (assumed 50%) the cost of outpatient care for long-bone fractures for 3 months (£5,073), assumed to be incurred by 61% of patients with non-vertebral fractures (total of £5,073 * 61% = £3,095) (based on Ross et al. set of assumptions)
Radiation to the bone	683	622	791	Average of HRG codes SC21Z, SC22Z, SC23Z, SC24Z, SC25Z, SC26Z, SC27Z, SC28Z weighted by the number of activity units in each HRG. NHS reference costs 2012-2013, Radiotherapy (RAD). 5 fractions are given.
Surgery to the bone	3,568	2,194	4,482	NHS reference costs 2012-2013; NEI_L: Weighted average of HD39E

Abbreviations: HRG: healthcare resource group; NHS: National Health Service; SRE: skeletal related event

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the

choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The key uncertainties around structural assumptions and parameter uncertainties relate to:

- The impact of treatment switching on OS estimates
- The parametric fitting of the OS and TTD/rPFS data
- The definition of treatment progression
- Limitations of the naive treatment comparison against abiraterone
- The UK treatment pathway
- Resource utilisation
- Potential double counting of disutilities for AEs and SREs

The scenario analyses conducted to investigate these uncertainties as well as the methods to perform each analysis are described in Table B79.

Table B79 Scenario analyses

	Analysis	Rationale / methods
	Data cut-off date	
1	Data cut-off September 2013	This date corresponds to the protocol pre-defined interim analysis2.This scenario is conducted to investigate what the impact of the original data cut-off would be. In this scenario the September data is used for OS (IPCW adjusted) and TTD; all other data was kept as for the base case.
	Survival modelling	
2	Two stage OS adjustment method	OS adjustment was also performed using the two stage method. The two stage method is one of the methods that can be used for PREVAIL data.
3	Unadjusted survival data	In the base case, the OS data was adjusted to correct for post-study treatments that are not available in clinical practice. When the treatment switching takes place, the ITT analysis may underestimate the true clinical benefit of the study drug. To show the impact of the adjustment on the ICER, an unadjusted analysis

	Analysis	Rationale / methods
		was also performed. All parameters were kept to their base case values, but parametric survival functions fit to the unadjusted data were used to model OS. The data cut-off used was still June 2014.
4	Gamma distribution for OS	The best statistical fit for the OS - Gamma - results in (clinically unrealistically) crossing tails. To show the impact of the curves crossing on the ICER, a scenario using the Gamma distribution was analysed.
5	Proportional hazards	In PREVAIL the proportionality of hazards did not hold, and therefore in the base case OS for enzalutamide and BSC was modelled using separate curves. However, hazard rates were proportional over most of the survival follow-up period2. It can also been argued that the proportionality did not hold due to the impact of 3rd line treatment. Although the IPCW analysis corrected for 2nd line treatment not available in England and Wales, no correction for 3rd line treatment was applied. To test what the impact would be if hazard rates were proportional a scenario was explored where the enzalutamide OS was modelled by applying a HR to the BSC curve.
6	Adjusted indirect comparison for abiraterone OS	At present the role of corticosteroids when given alone to chemo-naïve mHRPC patients is not clear. As discussed in sections 6.7.2 and 6.7.3, the use of corticosteroids in the comparator arm of PREVAIL and COU-AA-302 was markedly different (100% in COU-AA-302 vs 30.2% of patients received corticosteroids at some stage during the study in the control arm of PREVAIL). For this reason, the base case uses a naïve comparison for abiraterone. However, as steroids are shown to especially impact PFS, a scenario is also included using an adjusted indirect comparison for OS, and a naïve comparison for PFS.
	Progression modelling	
7	rPFS instead of TTD	A scenario with rPFS as a definition for PFS is included as rPFS is the one of primary endpoints in PREVAIL and also because no TTD data is available for abiraterone
8	Weibull distribution for TTD	UK experts selected a Weibull model for the OS and a Gamma model for PFS curves, due to the more realistic shape of the tail. The Weibull model for the PFS was only marginally different from the Gamma. The impact of the Weibull distribution was assessed in a scenario.
	Costs	
9	BNF price for docetaxel	In the base case the eMit database[144] is used as a source for the docetaxel price (£47.30 per 160mg/8ml solution for infusion vial). However, a scenario with the BNF price[143] for docetaxel (£1008.54 per 160mg/8ml solution for infusion vial) was also conducted. This scenario includes the list price for docetaxel, not including potential discounts and rebates.
10	Including unscheduled costs as per abiraterone submission to NICE	PREVAIL did not capture data on resource utilisation. Abiraterone's submission to NICE did include unscheduled resource utilisation. A scenario using data on unscheduled costs from abiraterone's submission to NICE was explored.
11	Including a 10.36% price rebate as per PPRS agreement for 2015	The 2015 payment percentage is 10.36%, and is expected to further increase to 15% in 2016[162]. However, for the purpose of this scenario, the

	Analysis	Rationale / methods
		conservative estimate of 10.36% was used, and applied as a discount to all drug acquisition costs.
12	Increased costs for spinal cord compression	In the model the NHS reference costs 2012-2013 data was used to derive costs for a spinal cord compression. UK experts asserted that the spinal cord compression may have higher costs. They also mentioned that approximately 1/5 of patients with spinal cord compression would need long-term care because of paraplegia
	Treatment pathway	
13	Abiraterone is given after docetaxel in the BSC arm	Although in clinical practice patients could receive either enzalutamide or abiraterone after docetaxel, for simplicity, the model assumes all patients receive enzalutamide. A scenario with abiraterone given after docetaxel in the BSC arm was explored.
	SREs	
14	Increase duration of SREs	UK experts indicated that SREs may last longer than currently is implemented in the model
	Utilities	
15	Baseline utility from AFFIRM is used for PP2 health state	AFFIRM is an alternative source for the PP2 health state utility as the AFFIRM population is post-docetaxel mHRPC patients
	AEs	
16	No disutulity and no costs for AEs	As most AEs have a duration <2 weeks, whereas QoL was measured every 12 weeks, it is unlikely that the impact of AEs was captured in the on treatment benefit. However, there may be a potential double-counting. By excluding the impact of AEs, any potential double counting is excluded
	Drug Costs	
17	Acquisition Costs varied	Patient Access Schemes provide discounts on drug prices

Abbreviations: AE: adverse event; OS: overall survival; PFS: progression free survival; QoL: quality of life; SRE: skeletal related events.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

All model inputs were varied in one-way sensitivity analyses (OWSA). Although most parameters were varied over their lower and upper 95% confidence level, some values were varied over extreme ranges to show the impact of the parameter (i.e., discount rate, time horizon). The ranges used for the parameters are presented in Appendix 14, section 10.14.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was performed on the base case using 10,000 Monte Carlo simulations. All distributions for the probabilistic analysis are shown in section 7.3.6. The results of the probabilistic analysis are shown in section 7.7.8.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B70 shows the clinical outcomes of the model compared with the trial results. It should be noted that the table shows the median values, whereas the development of the survival functions took into account all observations, as well as plausibility of the extrapolation. All median model values are within the 95% CI of the PREVAIL results.

Median TTD in the model was slightly longer than in the trial. As shown in the K-M overlay for TTD (Extrapolation report, Figure A.3. 5) TTD still includes some impact from the scanning frequency (every 12 weeks), shown as drops in the curve. Due to these drops, the model medians can vary slightly from the reported medians.

Also the OS Weibull curve showed a good fit to the observed data in the K-M overlays extrapolation report (Figure A.3. 11). Due to smaller number at risk towards the end of the curve, the curve shows a staircase pattern around the median for enzalutamide OS, which explains the small variation.

No data for TTD with abiraterone is currently available. In the model we use the latest rPFS published for abiraterone[82] as a proxy for TTD.

In terms of abiraterone's OS, the model results are largely in line with the trial results. As can be seen in appendix 17 (section 10.17), the median was reached after a very steep drop in the curve most likely after only one event. The modelled curve follows the data very well up to the point in time where there is very few patients at risk. As the modelled curve has a gradual decline whereas the original KM shows a sudden drop, there is a small difference between the trial and the modelled medians.

Table B80 Summary of model results compared with clinical data

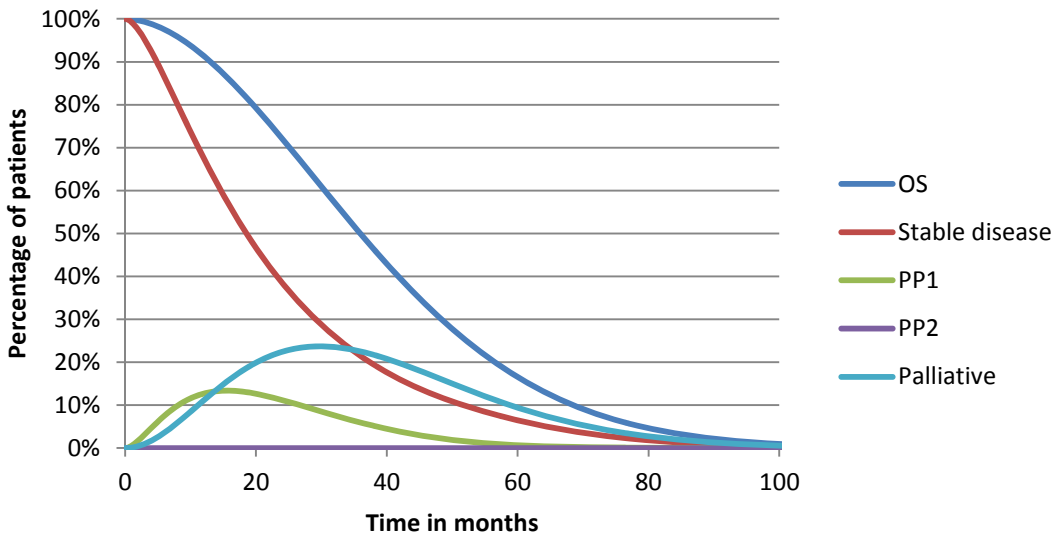
Outcome	Clinical trial result, months (median, 95% CI)	Model result, months (median)	Source
BSC			
TTD	[redacted]	[redacted]	Extrapolation report[81]
OS	[redacted]	[redacted]	OS adjustment report [37]
Enzalutamide			
TTD	[redacted]	[redacted]	Extrapolation report[81]
OS	[redacted]	[redacted]	OS adjustment report [37]
Abiraterone			
TTD	16.5*	15.36	Rathkopf 2014[82]
OS	35.3	33.77	Rathkopf 2014[82]

*TTD for abiraterone is not available from the literature. Thus the value included corresponds to rPFS as assessed by the investigator.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

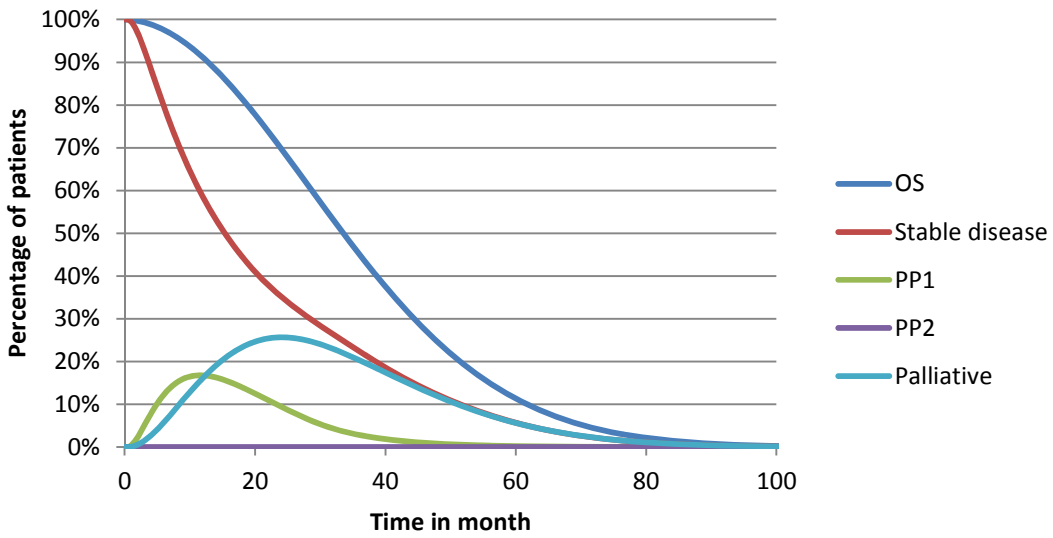
Markov traces for enzalutamide and its comparators are provided in Figure B18 to Figure B21. Patients treated with enzalutamide remain longer in the Stable Disease health state than patients on abiraterone or BSC. The benefit of enzalutamide is also illustrated by the longer time to death. As can be seen from these figures, the PP2 treatment state is only applicable for the BSC arm. Once progressed in the PP1 treatment state, patients in the enzalutamide and abiraterone arms move directly to palliative care.

Figure B19 Markov trace for enzalutamide



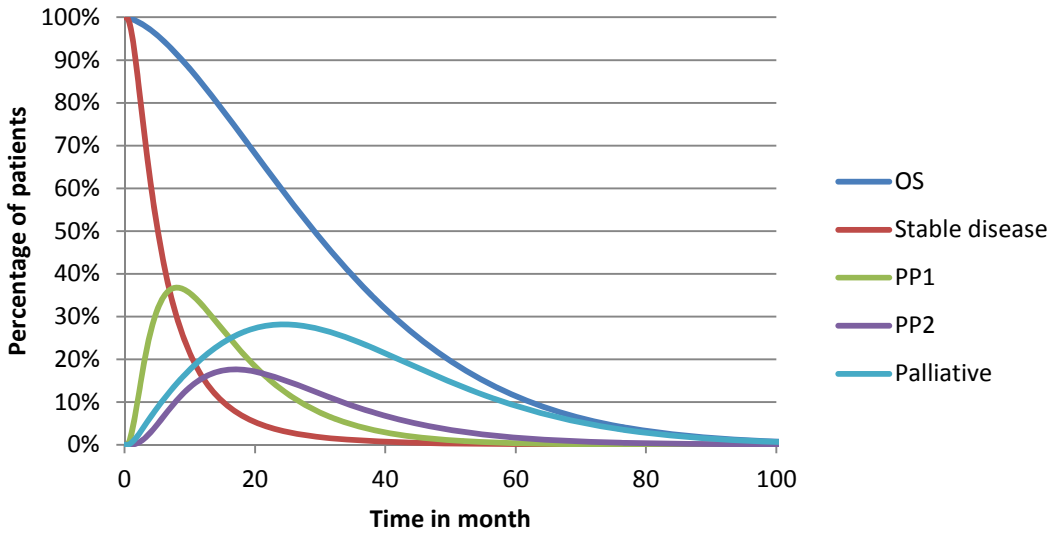
Abbreviations: OS: overall survival; PP1: post-progression 1; PP2: post-progression 2

Figure B20 Markov trace for abiraterone



Abbreviations: OS: overall survival; PP1: post-progression 1; PP2: post-progression 2

Figure B21 Markov trace for BSC



Abbreviations: OS: overall survival; PP1: post-progression 1; PP2: post-progression 2

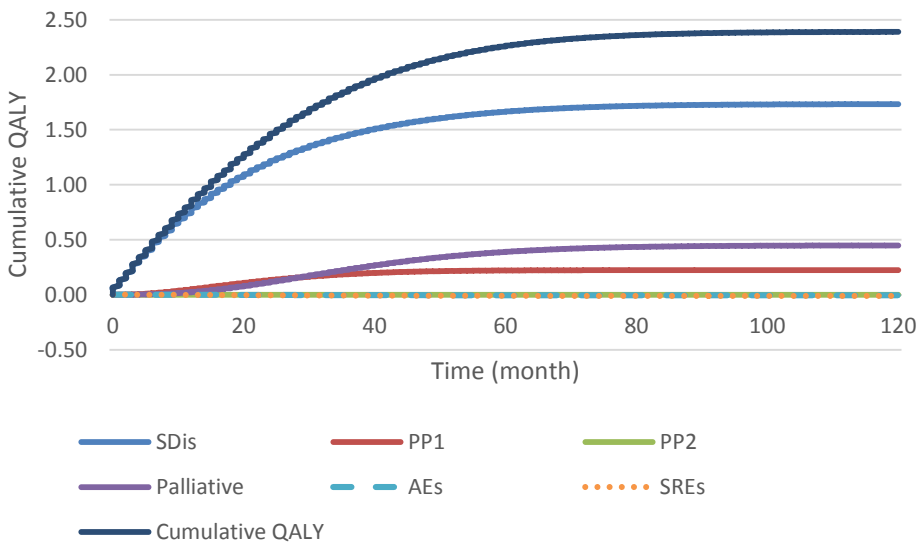
7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

QALY gain over time for all comparators is shown in Figure B22 to Figure B23. QALYs are accrued in the Stable Disease health state (blue line) and the Progressive Disease treatment states (PP1, PP2 and palliative care – red, green and purple

lines). QALY decrements as a result of AEs and SREs are also shown in the graphs (light blue and orange lines). The total QALYs gained over time is shown by the dark blue line. Please note that the QALY over time in these graphs is not discounted.

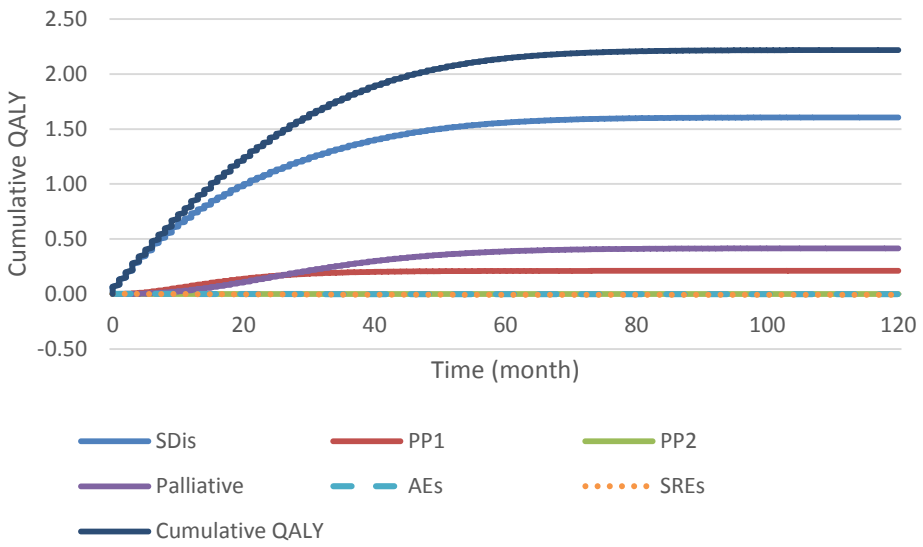
In line with patients treated with enzalutamide having a longer time in Stable Disease, and a higher on treatment utility than patients treated with the comparators, enzalutamide results in more QALYs gained in the Stable Disease health state. As the overall incidence and duration of the AEs and SREs is low, their impact is relatively small. Enzalutamide results in the highest cumulative QALYs as a result of longer OS and PFS, and due to the higher on treatment utility gain (versus BSC).

Figure B22 QALY gain over time with enzalutamide



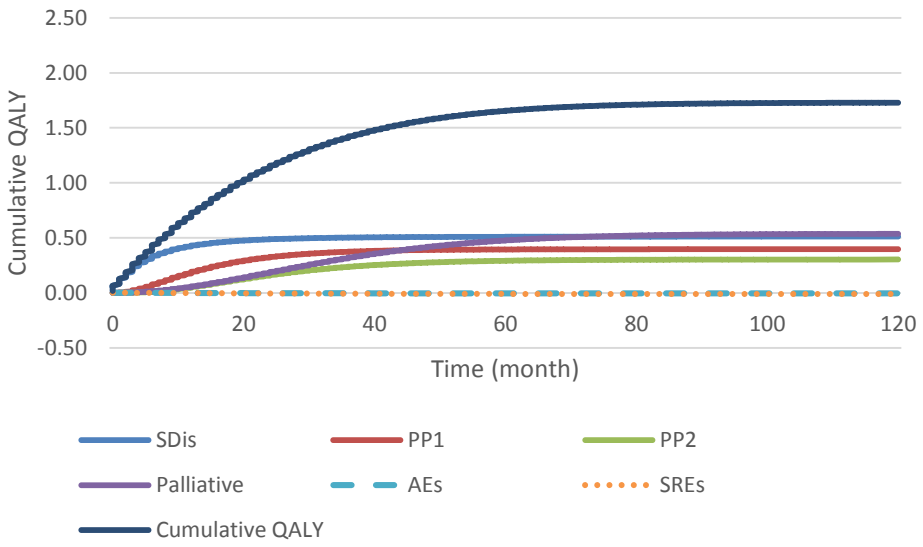
Abbreviations: AE: adverse event; PP1: post progression 1; PP2: post progression 2; QALY: quality-adjusted life year; SDis: stable disease; SRE: skeletal related event.

Figure B23 QALY gain over time with abiraterone



Abbreviations: AE: adverse event; PP1: post progression 1; PP2: post progression 2; QALY: quality-adjusted life year; SDis: stable disease; SRE: skeletal related event.

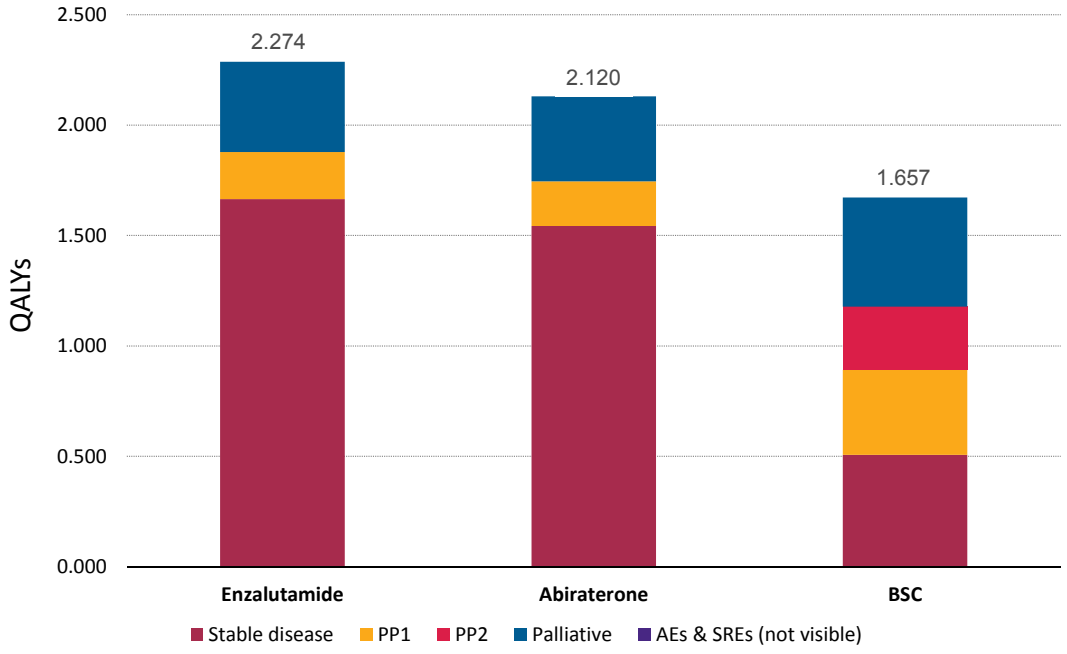
Figure B24 QALY gain over time with BSC



Abbreviations: AE: adverse event; PP1: post progression 1; PP2: post progression 2; QALY: quality-adjusted life year; SDis: stable disease; SRE: skeletal related event.

Figure B25 present the QALYs accumulated per health state over the entire model horizon. The vast majority of QALYs comes from the stable and progressed disease health states. Disutilities as a result of AEs and SREs have a minor impact. Overall, enzalutamide is associated with the highest total QALYs (2.274), followed by abiraterone (2.120). BSC is associated with the lowest QALYs of 1.657.

Figure B25 Effectiveness outcomes (discounted QALYs)



7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table B81 to Table B83 below display the discounted life years and QALYs accrued for each clinical outcome.

Table B81 Model outputs by clinical outcomes with enzalutamide

Outcome	LY	QALY	Cost (£)
Stable Disease	1.923	1.665	71,136
PP1	0.324	0.213	4,400
PP2	0.000	0.000	0
Palliative	0.818	0.409	7,691
AEs	-	-0.003	319
SREs	-	-0.009	1,294
Total (Overall survival)	3.064	2.274	84,840

Abbreviations: AE: adverse event; LY: life year; PP1: post-progression 1; PP2: post-progression 2; SRE: skeletal related event; QALY: quality-adjusted life year.

Table B82 Model outputs by clinical outcomes with abiraterone

Outcome	LY	QALY	Cost (£)
Stable Disease	1.782	1.543	67,556
PP1	0.309	0.203	4,194
PP2	0.000	0.000	0
Palliative	0.769	0.385	7,459
AEs	-	-0.002	253
SREs	-	-0.009	1,210
Total (Overall survival)	2.860	2.120	80,672

Abbreviations: AE: adverse event; LY: life year; PP1: post-progression 1; PP2: post-progression 2; SRE: skeletal related event; QALY: quality-adjusted life year.

Table B83 Model outputs by clinical outcomes with BSC

Outcome	LY	QALY	Cost (£)
Stable Disease	0.601	0.507	1,352
PP1	0.586	0.385	7,959
PP2	0.438	0.286	16,340
Palliative	0.988	0.494	8,666
AEs	-	-0.004	417
SREs	-	-0.011	1,562
Total (Overall survival)	2.612	1.657	36,296

Abbreviations: AE: adverse event; LY: life year; PP1: post-progression 1; PP2: post-progression 2; SRE: skeletal related event; QALY: quality-adjusted life year.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B84 Summary of QALY gain by health state - enzalutamide vs abiraterone

Health state	QALY ENZA	QALY ABI	Increment	Absolute increment	% absolute increment
Stable Disease	1.665	1.543	0.122	0.122	77.2%
PP1	0.213	0.203	0.010	0.010	6.3%
PP2	0.000	0.000	0.000	0.000	0.0%
Palliative	0.409	0.385	0.024	0.024	15.3%
AEs	-0.003	-0.002	-0.001	0.001	0.8%
SREs	-0.009	-0.009	-0.001	0.001	0.4%
Total	2.274	2.120	0.154	0.158	100%

Abbreviations: ABI: abiraterone; AE: adverse event; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Table B85 Summary of QALY gain by health state - enzalutamide vs BSC

Health state	QALY ENZA	QALY BSC	Increment	Absolute increment	% absolute increment
Stable Disease	1.665	0.507	1.158	1.158	68.0%
PP1	0.213	0.385	-0.172	0.172	10.1%
PP2	0.000	0.286	-0.286	0.286	16.8%
Palliative	0.409	0.494	-0.085	0.085	5.0%
AEs	-0.003	-0.004	0.001	0.001	0.0%
SREs	-0.009	-0.011	0.002	0.002	0.1%
Total	2.274	1.657	0.618	1.704	100%

Abbreviations: AE: adverse event; BSC: best standard of care; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Table B86 Summary of costs by health state - enzalutamide vs abiraterone

Health state	Cost ENZA (£)	Cost ABI (£)	Increment (£)	Absolute increment (£)	% absolute increment
Stable Disease	71,136	67,556	3,580	3,580	85.9%
PP1	4,400	4,194	205	205	4.9%
PP2	0	0	0	0	0.0%
Palliative	7,691	7,459	232	232	5.6%
AEs	319	253	66	66	1.6%
SREs	1,294	1,210	84	84	2.0%
Total	84,840	80,672	4,168	4,168	100%

Abbreviations: ABI: abiraterone; AE: adverse event; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Table B87 Summary of costs by health state - enzalutamide vs BSC

Health state	Cost ENZA (£)	Cost BSC(£)	Increment (£)	Absolute increment (£)	% absolute increment
Stable Disease	71,136	1,352	69,784	69,784	76.7%
PP1	4,400	7,959	-3,559	3,559	3.9%
PP2	0	16,340	-16,340	16,340	18.0%
Palliative	7,691	8,666	-975	975	1.1%
AEs	319	417	-99	99	0.1%
SREs	1,294	1,562	-268	268	0.3%
Total	84,840	36,296	48,543	91,024	100%

Abbreviations: AE: adverse event; BSC: best standard of care; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Table B88 Summary of predicted resource use by category of cost - enzalutamide vs abiraterone

Item	Cost ENZA (£)	Cost ABI (£)	Increment (£)	Absolute increment	% absolute increment
Active treatment - Stable Disease	68,213	63,203	5,010	5,010	70.2%
Concomitant medication - Stable Disease	683	659	23	23	0.3%
Health state - Stable Disease	2,240	3,693	-1,454	1,454	20.4%
Medication - PP1	251	239	12	12	0.2%
Concomitant medication - PP1	1,207	1,151	56	56	0.8%
Health state - PP1	1,244	1,186	58	58	0.8%
Medication - PP2	0	0	0	0	0.0%
Concomitant medication - PP2	0	0	0	0	0.0%
Health state - PP2	0	0	0	0	0.0%
Concomitant medication - Palliative	0	0	0	0	0.0%
Health state - Palliative	4,414	4,154	261	261	3.7%
Chemotherapy administration	1,698	1,619	79	79	1.1%
Terminal care	3,277	3,306	-29	29	0.4%
AEs	319	253	66	66	0.9%
SREs	1,294	1,210	84	84	1.2%
Total	84,840	80,672	4,168	7,132	100%

Abbreviations: ABI: abiraterone; AE: adverse event; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Table B89 Summary of predicted resource use by category of cost - enzalutamide vs BSC

Item	Cost ENZA (£)	Cost BSC (£)	Increment (£)	Absolute increment	% absolute increment
Active treatment - Stable Disease	68,213	0	68,213	68,213	74.9%
Concomitant medication - Stable Disease	683	213	470	470	0.5%
Health state - Stable Disease	2,240	1,139	1,101	1,101	1.2%
Medication - PP1	251	454	-203	203	0.2%
Concomitant medication - PP1	1,207	2,183	-976	976	1.1%
Health state - PP1	1,244	2,250	-1,006	1,006	1.1%
Medication - PP2	0	15,618	-15,618	15,618	17.2%
Concomitant medication - PP2	0	156	-156	156	0.2%
Health state - PP2	0	565	-565	565	0.6%
Concomitant medication - Palliative	0	0	0	0	0.0%
Health state - Palliative	4,414	5,334	-920	920	1.0%
Chemotherapy administration	1,698	3,071	-1,374	1,374	1.5%
Terminal care	3,277	3,332	-55	55	0.1%
AEs	319	417	-99	99	0.1%
SREs	1,294	1,562	-268	268	0.3%
Total	84,840	36,296	48,543	91,024	100%

Abbreviations: AE: adverse event; BSC: best standard of care; ENZA: enzalutamide; PP1: post progression 1; PP2: post progression 2; SRE: skeletal related event; QALY: quality-adjusted life year

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The results of the base case analysis are presented in Table B90. Abiraterone has an ICER of £95,685 against BSC. Enzalutamide has an ICER of £27,076 against abiraterone and £78,587against baseline (BSC). A comparison of these results with those from other economic evaluations is provided in section 7.10.1.

Table B90 Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
A: BSC	36,296	2.612	1.657	0	0	0	Not applicable	Not applicable
B: ABI	80,672	2.860	2.120	44,375	0.248	0.464	£95,685	Extended dominance by ENZA
C: ENZA	84,840	3.064	2.274	48,543	0.452	0.618	£78,587	£78,587 vs. BSC (£27,076 vs. ABI)

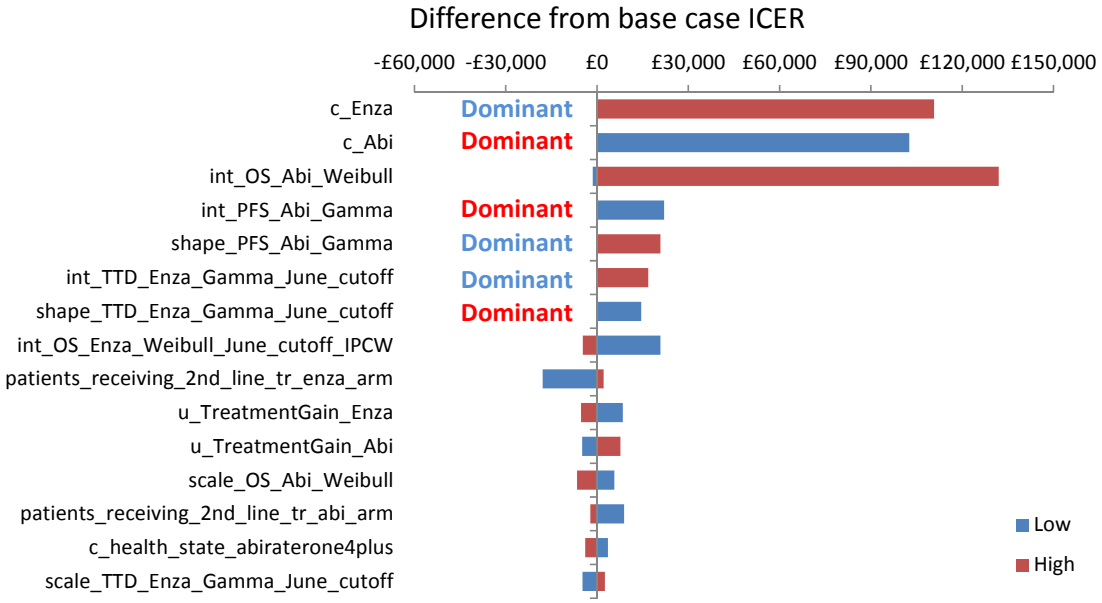
Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure B26 and Figure B27 below present the results of the deterministic sensitivity analysis using ICERs sorting. However, when the results include negative ICERs (dominant or dominated), the net benefit sorting can be preferred as the ICER spread may not accurately reflect the difference in decision making. Tornado diagrams using the net benefit sorting are presented in appendix 18 (section 10.18).

Figure B26 Tornado diagram for enzalutamide vs abiraterone



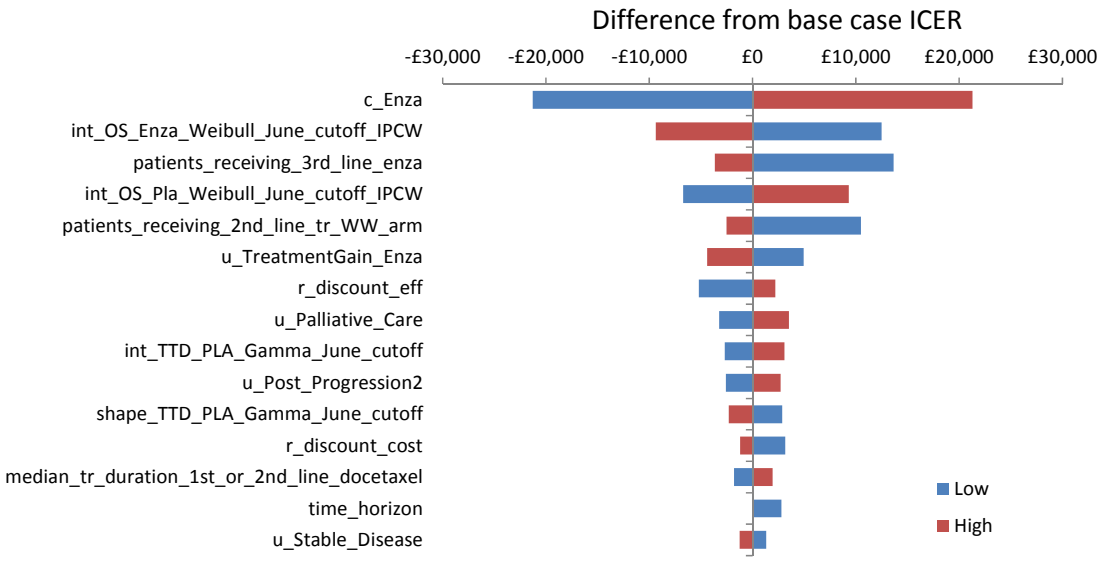
*It should be noted that the impact of correlated parameters (such as intercept and scale) should be interpreted with caution as only one parameter at a time is varied in this analysis, thus overestimating the actual impact.

Table B91 Description of ten most influential parameters in model for comparison enzalutamide vs abiraterone

Name	Description	Model input (low; high)	ICER low; high (£/QALY)
Base case			**9,174**
c_Enza	Enzalutamide costs	97.67 [73.25; 122.08]	Dominant (-83,706); 137,858
c_Abi	Abiraterone costs	97.67 [73.25; 122.08]	129,721; Dominant (-75,569)
int_OS_Abi_Weibull	Intercept of OS Weibull model abiraterone	[redacted]	25,706; 159,078
int_PFS_Abi_Gamma	Intercept of PFS Gamma model abiraterone	[redacted]	49,170; Dominant (-43,065)
shape_PFS_Abi_Gamma	Shape of PFS Gamma model abiraterone	[redacted]	Dominant (-26,806); 47,922
int_TTD_Enza_Gamma_June_cutoff	Intercept of TTD Gamma model for enzalutamide for June 2014 cut-off date	[redacted]	Dominant (-7,367); 43,921
shape_TTD_Enza_Gamma_June_cutoff	Shape of TTD Gamma model for enzalutamide for June 2014 cut-off date	[redacted]	41,601; Dominant (-576)
int_OS_Enza_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for enzalutamide for June 2014 cut-off date using IPCW adjustment method	[redacted]	47,881; 22,406
patients_receiving_2nd_line_tr_enza_arm	Proportion of patients receiving 2nd line chemotherapy in enzalutamide arm	0.84 [0.00; 1.00]	9,191; 29,183
u_TreatmentGain_Enza	Utility gain associated with pre-chemo treatment with enzalutamide	0.02 [0.00; 0.04]	35,500; 21,883

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; IPCW: inverse probability of censoring weights; QALY: quality adjusted life year.

Figure B27 Tornado diagram for enzalutamide vs BSC



*It should be noted that the impact of correlated parameters (such as intercept and scale) should be interpreted with caution as only one parameter at a time is varied in this analysis, thus overestimating the actual impact

Table B92 Description of ten most influential parameters in model for comparison enzalutamide vs BSC

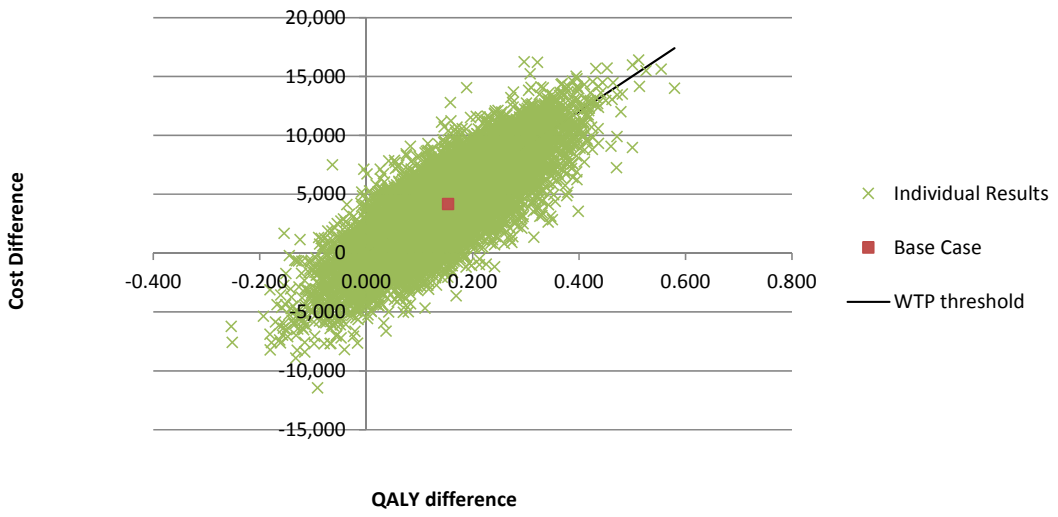
Name	Description	Model input (low; high)	ICER low; high (£/QALY)
Base case			**31,756**
c_Enza	Enzalutamide costs	97.67 [73.25; 122.08]	57,300; 99874
int_OS_Enza_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for enzalutamide for June 2014 cut-off date using IPCW adjustment method	[redacted]	91,081; 69,227
patients_receiving_3rd_line_enza	Proportion of patients receiving enzalutamide as a 3rd line treatment	0.81 [0.00; 1.00]	92,221; 74,924
int_OS_Pla_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for BSC for June 2014 cut-off date using IPCW adjustment method	[redacted]	71,873; 87,888
patients_receiving_2nd_line_tr_WW_arm	Proportion of patients receiving 2nd line chemotherapy in the BSC arm	0.84 [0.00; 1.00]	89,069; 76,059
u_TreatmentGain_Enza	On-treatment utility gain for patients treated with enzalutamide	0.02 [0.00; 0.04]	83,527; 74,199
r_discount_eff	Discount rate for effect	0.035 [0; 0.05]	73,398; 80,791
u_Palliative_Care	Utility in the palliative care health state	0.50 [0.34; 0.66]	75,348; 82,117
int_TTD_PLA_Gamma_June_cutoff	Intercept of TTD Gamma model for BSC for June 2014 cut-off date	[redacted]	75,893; 81,672
u_Post_Progression2	Utility in the post-progression 2 health state	0.61 [0.56; 0.66]	75,999; 81,294

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; OS: overall survival; QALY: quality adjusted life year; TTD: time to treatment discontinuation

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

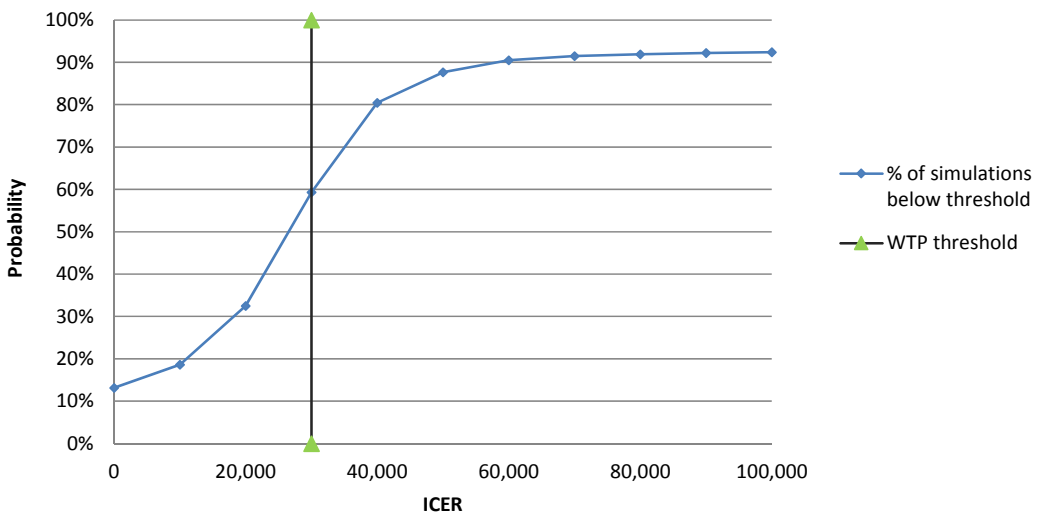
Scatter plots and cost-effectiveness acceptability curves (CEAC) are shown in Figure B28 to Figure B31. A summary of the PSA results, and a comparison with the deterministic results is provided in Table B94 and Table B95. Willingness to pay (WTP) thresholds of 30,000 £/QALY are shown in each curve. The probability of being cost-effective at different WTP thresholds is shown in Table B93.

Figure B28 Results of 10,000 runs – enzalutamide vs abiraterone



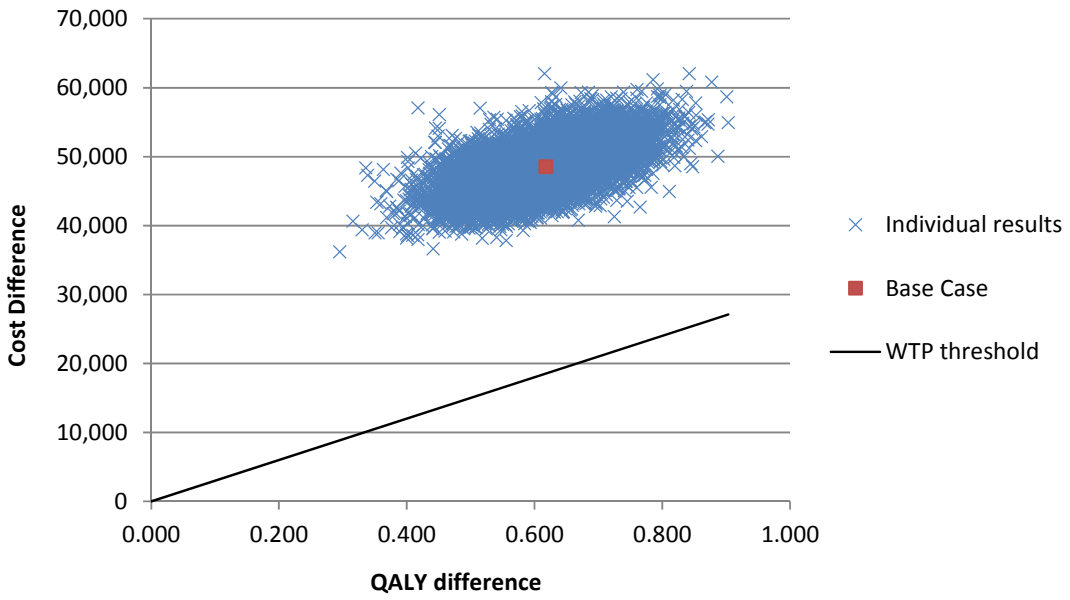
Abbreviations: QALY: quality adjusted life year; WTP: willingness to pay

Figure B29 CEAC enzalutamide vs abiraterone



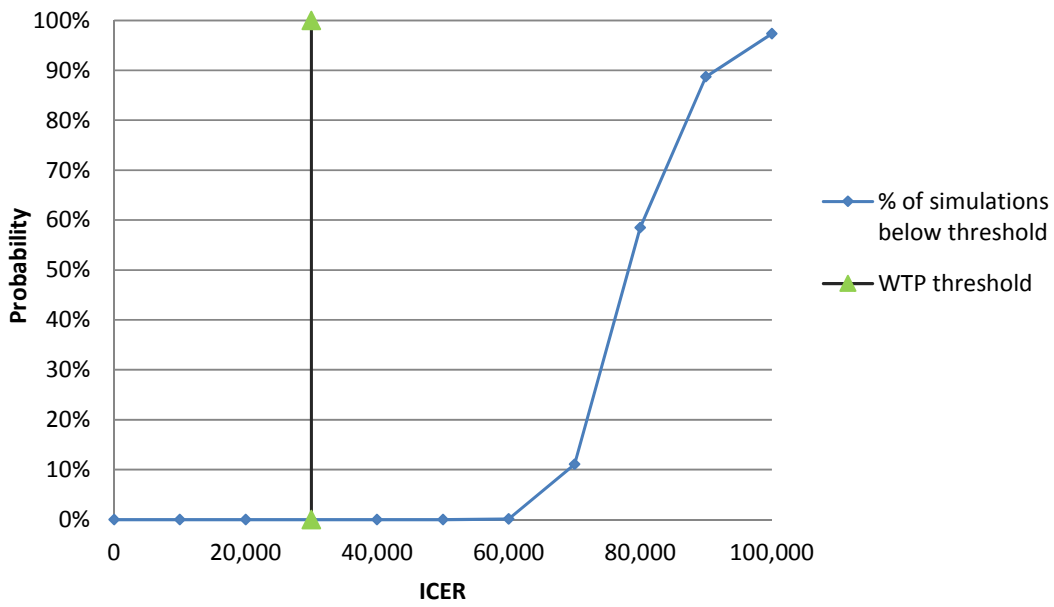
Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay

Figure B30 Results of 10,000 runs - enzalutamide vs BSC



Abbreviations: QALY: quality adjusted life year; WTP: willingness to pay

Figure B31 CEAC enzalutamide vs BSC



Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay

Table B93 Probability of being cost effective for all comparisons

WTP (£/QALY)	Probability of enzalutamide being cost effective against	
	ABI	BSC
20,000	33%	0%
30,000	59%	0%

Abbreviations: ABI: abiraterone; BSC: best supportive care; QALY: quality adjusted life year; WTP: willingness to pay

Table B94 Summary of probabilistic sensitivity analysis results – enzalutamide vs abiraterone

	Enzalutamide		Abiraterone		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Cohort	84,840	2.274	80,672	2.120	4,168	0.154	27,076
PSA	84,871	2.275	80,799	2.123	4,072	0.152	26,705
StDev	2,197	0.091	3,171	0.104	3,654	0.104	35,279
95%LCL	80,618	2.104	74,723	1.925	-3,222	-0.053	-
95%UCL	89,215	2.458	87,221	2.334	11,114	0.350	-
Min Limit	76,690	1.938	68,563	1.763	-11,444	-0.254	45,136
Max Limit	93,134	2.632	92,650	2.516	16,397	0.580	28,286

Abbreviations: LCL: lower confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; UCL: upper confidence level;

Table B95 Summary of probabilistic sensitivity analysis results – enzalutamide vs BSC

	Enzalutamide		BSC		Incremental		
	Costs	QALYs	Costs	QALYs	Costs	QALYs	CE ratio
Cohort	84,840	2.274	36,296	1.657	48,543	0.618	78,587
PSA	84,871	2.275	36,361	1.658	48,510	0.617	78,631
StDev	2,197	0.091	2,903	0.093	3,355	0.078	43,109
95%LCL	80,618	2.104	30,504	1.478	42,113	0.461	65,966
95%UCL	89,215	2.458	41,919	1.841	55,376	0.765	100,458
Min Limit	76,690	1.938	24,262	1.290	36,235	0.295	122,814
Max Limit	93,134	2.632	46,708	1.992	62,067	0.904	68,689

Abbreviations: BSC: best supportive care; LCL: lower confidence level; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life year; UCL: upper confidence level.

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses are shown in Table B96 and the rationale for each analysis were described in Table B79. The methodology used to run the scenario analyses described in Appendix 16 (section 10.16).

Table B96 Results of scenario analyses

	Analysis	ICER Enzalutamide vs Abiraterone (£)	ICER Enzalutamide vs BSC (£)
	Base case	**27,076**	**78,587**
	Data cut-off date		
1	Data cut-off September 2013	47,213	98,751
	Survival modelling		
2	Two stage OS adjustment method	39,399	87,677
3	Unadjusted survival data	33,291	97,185
4	Gamma distribution for OS	34,499*	90,019
5	Proportional hazards	40,187	69,377
6	Adjusted indirect comparison for abiraterone OS	Dominant (-4,510)	78,587
	Progression modelling		
7	rPFS (Sept) instead of TTD	28,894	86,696
	For comparison TTD (Sept)	28,642	81,449
8	Weibull distribution for TTD	30,404	78,317
	Costs		
9	BNF price for docetaxel	28,623	71,908
10	Including unscheduled costs as per abiraterone submission to NICE	29,006	75,159
11	Applying the PPRS payment percentage for 2015 (10.36%)	23,642	69,911
12	Increase costs for spinal cord compression	27,314	78,210
	Treatment pathway		
13	Abiraterone is given after docetaxel in the BSC arm	27,076	79,535
	SREs		
14	Increase duration of SREs	27,690	77,044
	Utilities		
15	Baseline utility from AFFIRM is used for PP2 health state	27,076	83,042
	AEs		
16	No disutulity and no costs for AEs	26,432	78,835
	Drug Costs		
17	Patient Access Scheme discounts available	Range of values – see table B122	Range of values – see table B122

Abbreviations: BNF: British National Formulary: ICER: incremental cost-effectiveness ratio; OS: overall survival; PH: proportional hazards; SRE: skeletal related event; TTD: time to treatment discontinuation; *Reversed ICER

7.7.10 What were the main findings of each of the sensitivity analyses?

As shown in section 7.7.8, enzalutamide has a 59% probability of being cost-effective against abiraterone a WTP threshold of £30,000 per QALY gained.

Uncertainty around input values was tested in the deterministic sensitivity analysis. The most influential model parameters were the costs of enzalutamide and

abiraterone as well as the on treatment utility gain derived from PREVAIL. Against BSC, other influential model parameters were the proportions of patients receiving 2nd and 3rd line of treatment. Overall, most parameters showed only a limited impact, and did not cross major cost-effectiveness thresholds. It should be noted that the impact of correlated parameters (such as intercept and scale) should be interpreted with caution as only one parameter at a time is varied in this analysis, thus overestimating the actual impact.

The impact of structural assumptions was included in the scenario analyses in section 7.7.9. The scenario analyses results vs BSC were fairly robust with ICERs ranging from £69,377/QALY to £97,185/QALY. The results were most sensitive to the assumptions of data cut-off date, survival modelling, docetaxel costs as well as unscheduled costs. Despite several uncertainties in the indirect comparison, most of the scenario analyses results vs abiraterone were also robust, however the base case ICER of enzalutamide vs abiraterone is more sensitive to structural assumptions than the ICER of enzalutamide vs BSC due to small differences between costs and effects between two treatments.

Scenario 1 - Data cut-off September 2013

Applying September 2013 data results in uncertain less reliable extrapolation of the survival curve. This leads to a shorter OS and PFS for enzalutamide and longer OS and PFS for BSC (Table B97), resulting in an ICER of £98,751/QALY compared to £78,587/QALY in the base case for the comparison vs BSC. The ICER vs abiraterone increases to £47,213/QALYcompared to the base case ICER of £27,076/QALY (Table B98).

Table B97 Scenario: September 2013 cut-off – clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	36.2	34.0	36.0	33.8	36.0	33.8	32.9	29.1	33.5	29.5
PFS (month)	24.0	18.6	23.7	18.7	22.2	15.4	22.2	15.4	7.3	5.1	7.9	5.0

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival.

Table B98 Scenario September 2013 cut-off – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£67,487	£63,203	£0
Other costs	£15,412	£17,469	£35,993
Total costs	£82,899	£80,672	£35,993
Incremental costs	-	£2,227	£46,905
LYG	2.872	2.860	2.657
LYG difference		0.012	0.215
QALYS	2.168	2.120	1.693
QALY difference		0.047	0.475
ICER (Cost/QALY gained)		£47,213	£98,751

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 2 - Two stage OS adjustment method

Application of the two stage method leads to a shorter OS for both enzalutamide and BSC, and does not affect abiraterone's clinical outcomes (Table B99). The ICER vs abiraterone increased from £27,076/QALY in the base case to £39,399/QALY in this scenario. A shorter OS for enzalutamide and BSC leads to an increase in the ICER vs BSC: £87,677/QALY compared to the base case ICER of £78,687/QALY (Table B100).

Table B99 Scenario Two stage OS adjustment method - clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	36.7	34.0	36.0	33.8	36.0	33.8	32.9	29.1	32.7	28.8
PFS (month)	24.0	18.6	23.8	18.6	22.2	15.4	22.2	15.4	7.3	5.1	7.3	5.1

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B100 Scenario Two stage OS adjustment method – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£67,693	£63,203	£0
Other costs	£15,598	£17,469	£36,079
Total costs	£83,290	£80,672	£36,079
Incremental costs	-	£2,618	£47,211
LYG	2.906	2.860	2.598
LYG difference		0.046	0.308
QALYS	2.187	2.120	1.648
QALY difference		0.066	0.538
ICER (Cost/QALY gained)		£39,399	£87,677

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 3 Unadjusted survival data

Using unadjusted data results in a shorter OS for enzalutamide and longer OS for BSC, and does not affect abiraterone's clinical outcomes (Table B101). Due to a shorter OS for enzalutamide in this scenario and therefore lower total costs, the ICER vs abiraterone increased from £27,076/QALY in the base case to £33,291/QALY in this scenario. The ICER vs BSC becomes higher in this scenario compared to the base case: £97,185/QALY vs £78,587/QALY in the base case (Table B102).

Table B101 Scenario Unadjusted survival data - clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	37.2	34.7	36.0	33.8	36.0	33.8	32.9	29.1	35.0	30.6
PFS (month)	24.0	18.6	23.8	18.6	22.2	15.4	22.2	15.4	7.3	5.1	7.3	5.1

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B102 Scenario Unadjusted survival data – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£67,711	£63,203	£0
Other costs	£15,897	£17,469	£37,529
Total costs	£83,609	£80,672	£37,529
Incremental costs	-	£2,937	£46,080
LYG	2.947	2.860	2.765
LYG difference		0.087	0.182
QALYS	2.209	2.120	1.735
QALY difference		0.088	0.474
ICER (Cost/QALY gained)		£33,291	£97,185

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 4 Gamma distribution for OS

Compared to the base case, the Gamma fit resulted in a slightly shorter OS for enzalutamide and longer OS and PFS for abiraterone, which lead to a reversed ICER vs abiraterone of £34,499/QALY (i.e. enzalutamide is less costly and less effective - Table B104). The results should be interpreted with care due to implausible extrapolation of Gamma curve (Gamma curves for enzalutamide and placebo cross early which results in less benefit for enzalutamide). Applying Gamma model to OS results a slightly longer OS for BSC (Table B103). This leads to a higher percentage of patients alive in the placebo arm than in the enzalutamide arm and to a higher ICER compared to the base case ICER (Table B104).

Table B103 Scenario Gamma distribution for OS - clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	37.8	35.8	36.0	33.8	40.6	34.8	32.9	29.1	34.5	29.0
PFS (month)	24.0	18.6	23.7	18.6	22.2	15.4	24.5	15.4	7.3	5.1	7.3	5.1

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival;

Table B104 Scenario Gamma distribution for OS – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£67,506	£68,686	£0
Other costs	£16,263	£18,719	£36,903
Total costs	£83,770	£87,405	£36,903
Incremental costs	-	-£3,635	£46,867
LYG	2.991	3.179	2.718
LYG difference		-0.189	0.273
QALYS	2.230	2.335	1.709
QALY difference		-0.105	0.521
ICER (Cost/QALY gained)		34,499*	£90,019

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year.
*Reversed ICER (the ICER which results from negative incremental costs and negative incremental QALYs – the 4th quadrant on a cost-effectiveness plane)

Scenario 5 - Proportional hazards

As shown in Table B105 and Table B106, application of the proportionality of hazards assumption results in longer OS and TTD for enzalutamide which leads to a higher ICER for enzalutamide vs abiraterone (£40,187/QALY compared to £27,076/QALY in the base case) and a lower ICER for enzalutamide vs BSC (£69,377/QALY compared to £78,587/QALY in the base case). The increase in the ICER vs abiraterone is due to limitation of the naive comparison.

Table B105 Scenario Proportional hazards – clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	43.0	38.2	36.0	33.8	36.0	33.8	32.9	29.1	32.9	29.1
PFS (month)	24.0	18.6	29.2	19.3	22.2	15.4	22.2	15.4	7.3	5.1	7.3	5.1

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B106 Scenario Proportional hazards – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£81,488	£63,203	£0
Other costs	£15,981	£17,469	£36,296
Total costs	£97,469	£80,672	£36,296
Incremental costs	-	£16,797	£61,173
LYG	3.347	2.860	2.612
LYG difference		0.486	0.734
QALYS	2.538	2.120	1.657
QALY difference		0.418	0.882
ICER (Cost/QALY gained)		£40,187	£69,377

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year.

Scenario 6 - Adjusted indirect comparison for abiraterone OS

In the base case enzalutamide and abiraterone are compared using a naïve treatment comparison. An alternative scenario using an adjusted indirect comparison for abiraterone's OS was explored. In this scenario an adjusted ITC was used only for OS, whereas a naïve comparison was used for rPFS as an application of an adjusted indirect comparison for abiraterone's rPFS would result in unrealistically short median PFS of 8.7 months (given the reported median PFS of 16.5 months[82]). This is a result of the differences between the control arms in PREVAIL and COU-AA-302 studies.

Use of an adjusted indirect comparison for abiraterone's OS did not affect clinical results of enzalutamide, whereas abiraterone has a slightly longer OS (Table B107) in this scenario which leads to higher total costs. This scenario results in enzalutamide being dominant over abiraterone (-£4,510/QALY) (Table B108).

Table B107 Scenario Adjusted indirect comparison for abiraterone OS - clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	38.9	35.9	36.0	33.8	38.2	33.8	32.9	29.1	32.9	29.1
PFS (month)	24.0	18.6	24.0	18.6	22.2	15.4	23.9	15.4	7.3	5.1	7.3	5.1

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B108 Scenario Adjusted indirect comparison for abiraterone OS – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£67,378	£0
Other costs	£16,626	£17,666	£36,296
Total costs	£84,840	£85,044	£36,296
Incremental costs	-	-£204	£48,543
LYG	3.064	2.999	2.612
LYG difference		0.065	0.452
QALYS	2.274	2.229	1.657
QALY difference		0.045	0.618
ICER (Cost/QALY gained)		Dominant (-4,510)	£78,587

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 7 - rPFS instead of TTD

In the base case TTD is used as the indicator of progression. The results of an alternative scenario using rPFS are presented below. As rPFS data are only available for the September cut-off, a second scenario is presented using September TTD for comparison. Using Sept rPFS as an indicator for progression instead of September TTD leads to a longer duration in stable disease for both enzalutamide and BSC (Table B109). This results in smaller incremental QALY and a small increase in incremental costs. The ICER vs. abiraterone using Sept rPFS was £28,894/QALY compared to £28,642/QALY using Sept TTD. The ICER vs. BSC using Sept rPFS was £86,696/QALY compared to £81,449/QALY using Sept TTD (Table B110 and Table B111).

Table B109 Scenario rPFS instead of TTD – clinical outcomes

	ENZA base case		ENZA scenario				ABI base case	
	June TTD		Sep rPFS		Sep TTD		rPFS 3rd IA	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	38.9	35.9	38.9	35.9	36.0	33.8
PFS (month)	24.0	18.6	24.1	19.8	24.2	18.7	22.2	15.4
	BSC base case		BSC scenario					
	June TTD		Sep rPFS		Sep TTD			
	Mean	Median	Mean	Median	Mean	Median		
OS (month)	32.9	29.1	32.9	29.1	32.9	29.1		
PFS (month)	7.3	5.1	9.0	6.5	7.9	5.0		

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B110 Scenario September rPFS – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,621	£63,203	£0
Other costs	£16,647	£17,469	£34,685
Total costs	£85,268	£80,672	£34,685
Incremental costs	-	£4,596	£50,584
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.280	2.120	1.696
QALY difference		0.159	0.583
ICER (Cost/QALY gained)		£28,894	£86,696

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Table B111 Scenario September TTD – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,645	£63,203	£0
Other costs	£16,546	£17,469	£35,639
Total costs	£85,191	£80,672	£35,639
Incremental costs	-	£4,519	£49,553
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.278	2.120	1.670
QALY difference		0.158	0.608
ICER (Cost/QALY gained)		£28,642	£81,449

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 8 - Weibull distribution for TTD

Compared to the base case, Weibull fit results in a slightly longer median PFS for all comparators (Table B112). This leads to an ICER vs abiraterone of £30,404/QALY compared to the base case ICER of £27,076/QALY, and vs BSC £78,317/QALY compared to £78,587/QALY in the base case, and vs (Table B113).

Table B112 Scenario Weibull distribution for TTD – clinical outcomes

	ENZA base case		ENZA scenario		ABI base case		ABI scenario		BSC base case		BSC scenario	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
OS (month)	38.9	35.9	38.9	35.9	36.0	33.8	36.0	33.8	32.9	29.1	32.9	29.1
PFS (month)	24.0	18.6	23.2	19.1	22.2	15.4	21.1	16.6	7.3	5.1	7.3	5.7

Abbreviations: BSC: best supportive care; ENZA: enzalutamide; OS: overall survival; PFS: progression free survival

Table B113 Scenario Weibull distribution for TTD – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£66,098	£60,192	£0
Other costs	£17,122	£18,141	£36,328
Total costs	£83,220	£78,332	£36,328
Incremental costs	-	£4,887	£46,891
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.257	2.096	1.658
QALY difference		0.161	0.599
ICER (Cost/QALY gained)		£30,404	£78,317

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 9 - BNF price for docetaxel

Using the BNF price for docetaxel results in the higher total costs mostly affecting the BSC arm. This leads to a lower ICER for enzalutamide vs BSC (£71,908/QALY vs the base case ICER of £78,587/QALY) and slightly higher ICER vs abiraterone (Table B114).

Table B114 Scenario BNF price for docetaxel – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£21,725	£22,330	£45,521
Total costs	£89,939	£85,533	£45,521
Incremental costs	-	£4,406	£44,418
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.657
QALY difference		0.154	0.618
ICER (Cost/QALY gained)		£28,623	£71,908

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 10 - Including unscheduled costs as per abiraterone submission to NICE

The application of unscheduled costs as per abiraterone submission to NICE leads to higher total costs for all comparators which results in an ICER of £29,006/QALY vs abiraterone (the base case ICER is £27,076/QALY), and £75,159/QALY vs BSC (the base case ICER is £78,587/QALY).

Table B115 Scenario Including unscheduled costs as per abiraterone submission to NICE – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£22,387	£22,932	£44,174
Total costs	£90,600	£86,135	£44,174
Incremental costs	-	£4,465	£46,426
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.657
QALY difference		0.154	0.618
ICER (Cost/QALY gained)		£29,006	£75,159

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 11 - Including a 10.36% price rebate as per PPRS agreement for 2015

This scenario resulted in lower total costs for all comparators leading to an ICER vs abiraterone of £23,642/QALY and an ICER vs BSC of £69,911/QALY (Table B116).

Table B116 Scenario Applying the PPRS payment percentage for 2015 (10.36%)

	ENZA	ABI	BSC
Technology acquisition cost	£61,146	£56,655	£0
Other costs	£16,405	£17,257	£34,367
Total costs	£77,551	£73,912	£34,367
Incremental costs	-	£3,639	£43,184
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.657
QALY difference		0.154	0.618
ICER (Cost/QALY gained)		£23,642	£69,911

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 12 - Increased costs for spinal cord compression

This scenario resulted in marginal changes in the base case ICER (Table B117).

Table B117 Scenario Increased costs for spinal cord compression – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£17,204	£18,010	£37,107
Total costs	£85,417	£81,212	£37,107
Incremental costs	-	£4,205	£48,310
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.657
QALY difference		0.154	0.618
ICER (Cost/QALY gained)		£27,314	£78,210

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 13 - Abiraterone is given after docetaxel in the BSC arm

As the cost of abiraterone is the same as the cost of enzalutamide, the results of this scenario are only marginally differ from the base case due to some differences between enzalutamide and abiraterone in resource use (Table B118).

Table B118 Scenario Abiraterone is given in PP2 (BSC arm)

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£16,626	£17,469	£35,180
Total costs	£84,840	£80,672	£35,180
Incremental costs	-	£4,168	£49,659
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.650
QALY difference		0.154	0.624
ICER (Cost/QALY gained)		£27,076	£79,535

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 14 - Increased duration of SREs

This scenario resulted in an ICER vs abiraterone of £27,690 compared to the base case ICER of £27,076. The scenario ICER vs BSC is £77,044/QALY compared to the base case ICER of £78,587/QALY (Table B119).

Table B119 Scenario Increased duration of SREs – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£16,626	£17,469	£36,296
Total costs	£84,840	£80,672	£36,296
Incremental costs	-	£4,168	£48,543
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.220	2.069	1.589
QALY difference		0.151	0.630
ICER (Cost/QALY gained)		£27,690	£77,044

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 15 - Baseline utility from AFFIRM is used for PP2 health state

As the PP2 health state is only applicable for the BSC arm, the ICER vs abiraterone is not affected in this scenario. The ICER vs BSC becomes slightly higher than in the base case (£78,835/QALY vs £78,587 per QALY) due to the higher utility value in the PP2 health state (Table B120).

Table B120 Scenario Baseline utility from AFFIRM is used for PP2 health state – cost-effectiveness results

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£16,626	£17,469	£36,296
Total costs	£84,840	£80,672	£36,296
Incremental costs	-	£4,168	£48,543
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.274	2.120	1.690
QALY difference		0.154	0.585
ICER (Cost/QALY gained)		£27,076	£83,042

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 16 - No disutility and no costs for AEs

This scenario showed that the model is relatively insensitive to the utility decrement and costs for AEs, which shows that potential double counting in utility values is not likely to have a big impact on the cost-effectiveness results (Table B121).

Table B121 Scenario No disutility and no costs for AEs

	ENZA	ABI	BSC
Technology acquisition cost	£68,213	£63,203	£0
Other costs	£16,308	£17,216	£35,879
Total costs	£84,521	£80,419	£35,879
Incremental costs	-	£4,102	£48,642
LYG	3.064	2.860	2.612
LYG difference		0.204	0.452
QALYS	2.278	2.122	1.661
QALY difference		0.155	0.617
ICER (Cost/QALY gained)		£26,432	£78,835

Abbreviations: ABI: abiraterone; BSC: best supportive care; ENZA: enzalutamide; LYG: life year gained; QALY: quality-adjusted life year

Scenario 17 – Comparison versus abiraterone while varying its PAS discount in 5% increments and keeping enzalutamide discount to [redacted]

Table B122 Results versus abiraterone while varying its PAS discount in 5% increments

Price discount ABI	Total Costs ENZA	Total Costs ABI	Incr. Costs	Incr. Effects	ICER (£/QALY)	Dominant ICER
0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI: abiraterone; ENZA: enzalutamide; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

Figure B32 [redacted]

[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme

In conclusion, the sensitivity analyses showed that the health economic model provides robust results, with a limited influence of either parameter inputs, or structural assumptions.

7.7.11 What are the key drivers of the cost-effectiveness results?

As described in section 7.7.10, key drivers of the cost-effectiveness results against abiraterone are the costs of enzalutamide and abiraterone as well as the on treatment utility gain which was derived from PREVAIL.

Against BSC key drivers of the cost-effectiveness results are the costs of enzalutamide, proportion of patients receiving 2nd and 3rd line of treatment in the BSC arm and the on treatment utility gain (derived from PREVAIL).

As described throughout this chapter, there is a substantial level of uncertainty regarding the relative efficacy of enzalutamide over abiraterone. The differences in the control arm of both studies justify a naïve comparison between enzalutamide and abiraterone. However, Astellas recognise the limitations of the naïve comparison as well and thus, uncertainty around the corresponding efficacy input values was tested in the deterministic sensitivity analysis and in different scenarios. Despite several uncertainties in the indirect comparison, most of the scenario analyses results vs abiraterone were robust. As observed in Figure B26, in general the model is only marginally sensitive to these input parameters.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The model programming was internally validated by an experienced health economist not involved in the project. Extreme value scenarios were performed, as well as validation of internal consistency, face validity and source validation of input data. The modelling methods and results were also reviewed by an external health economic expert.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis has been conducted for the current submission.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Not applicable.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No economic evaluations have been published for enzalutamide for the treatment of mHRPC for patients in whom chemotherapy is not yet clinically indicated.

For NICE's ongoing technology appraisal of abiraterone in this indication, the manufacturer submitted an economic model comparing abiraterone to BSC[35]. In the company's deterministic base-case analysis, the estimated ICER was £46,722 per QALY gained vs. BSC and the ERG presented an exploratory base case of £57,300 per QALY gained vs. BSC. Based on the Astellas model presented here, the ICER of abiraterone vs BSC was £95,685 per QALY gained. It is difficult, however, to compare the results from both analyses directly, not in the least because of the different model structures: a discrete event simulation vs a Markov model for the economic evaluation of abiraterone and enzalutamide, respectively. Additionally the abiraterone dossier referred to here included a PAS discount, and this revised dossier does not.

The two economic evaluations also differed in the comparator used: this evaluation compared against BSC, whereas the abiraterone TA compared against prednisone. As we heard from clinical experts that corticosteroids are likely to impact PFS and OS, the different comparator may have resulted in the lower ICER for abiraterone in this evaluation.

The fact that important input parameters, including utility values and the patient access scheme, are CIC in the abiraterone submission further impedes a direct comparison.

Other differences between the two evaluations that may have further influenced the results, and hinder a comparison between the two evaluations are reported in Table B.

Table B123 Comparison of key model aspects differing between the abiraterone and enzalutamide submissions

Model Aspect	Abiraterone submission to NICE	Enzalutamide submission to NICE (this analysis)
Model structure	Discrete event simulation	Three state Markov model, in line with previous models in mHRPC
BSC as comparator	In COU-AA-302, all control patients received placebo plus prednisone.	In PREVAIL, use of corticosteroids was allowed but not required
Model population	• Patients with visceral metastases were excluded • Non-random subset of 902 out of the 1,088 ITT patients (83%) of COU-AA-302	• Patients with visceral metastases were included (12% of all patients) • PREVAIL ITT population
Adjustment for treatment switching	15% of the patients, those who did not follow the specified treatment pathways in the model were censored at the time they deviated from the pathway.	IPCW adjustment method was applied to correct for post-progression treatment switching in PREVAIL as recommended by NICE DSU

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, the economic evaluation includes the entire population of adult men with mHRPC who are asymptomatic or mildly symptomatic in whom chemotherapy is not yet clinically indicated. This population included patients with ECOG 0 or 1, and PSA and/or radiographic progression despite ADT[11,83].

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

One of the main strengths of the analysis is the comprehensive methods with which survival was modelled. The data was derived directly from PREVAIL, a robust clinical study among 1,717 mHRPC patients, and obtained after a long follow-up period. Both the survival extrapolation and adjustments made for treatment switching have been performed in accordance with guidance issued by the NICE DSU and have been validated by external experts. The model has been constructed to represent the UK situation by including all relevant treatment pathways and adjusting for post-progression treatments that are not available in the UK. Rather than using a naïve method (e.g. censoring), conceivably introducing selection bias, the robust methods that are preferred by the DSU have been used to adjust for treatment switching (i.e. IPCW and two stage method).

The model structure is transparent and in line with previous economic models in mHRPC. Extensive scenario and sensitivity analyses show that the results are robust, and that there is no single parameter or assumption driving the incremental cost-effectiveness results. Although the one-way sensitivity analysis showed that the parametric survival parameters were the important model parameters, it should be noted that their impact may be overestimated as the analysis does not take into account correlation between the intercept an scale.

Limitations

The comparison of enzalutamide to abiraterone is limited by the indirect treatment comparison. The key limitation relates to lack of a common comparator. In COU-AA-302 all patients received corticosteroids, whereas in PREVAIL only a small proportion received steroids during the course of the trial. Although the impact of steroids on OS is uncertain, we heard from clinical experts that steroids will likely effect PFS. Therefore, any adjusted indirect comparison is likely to be subject to bias. However, an ITC was conducted and the results have been tested in a scenario.

The studies have a relatively similar setting, design, and patient population and thus a naïve comparison was preferred to include abiraterone in the evaluation. Although the naïve comparison is not influenced by the different control arms it does not adjust for differences between the two trials, and therefore increases the uncertainty around the comparison with abiraterone. Scenario analyses with alternative assumptions showed enzalutamide either being dominant or at an ICER usually considered cost-effective against abiraterone.

Although the patient population in PREVAIL and COU-AA-302 is similar, PREVAIL included patients with visceral metastases, whereas these patients were excluded from the COU-AA-302 trial. The more advanced patient population in PREVAIL may bias this analysis against enzalutamide. However, including patients with visceral metastases could be considered representative of clinical practice.

Another limitation for the comparison with abiraterone is the lack of reported TTD data for this comparator. To overcome this, rPFS was used for abiraterone. A scenario analysis using rPFS data for enzalutamide and BSC showed results similar to the base case.

As discussed in section 7.3.1.2, the TTD endpoint was considered to more accurately reflect clinical practice and was used in the model for enzalutamide and BSC. However, it is unclear what treatment duration can be expected in clinical practice. Data from the European oncology monitoring in Q2 2014 indicated that the actual treatment duration for enzalutamide and abiraterone in the chemo-naïve setting may be shorter in clinical practice than in clinical trials. This would lead to lower treatment costs.

Although an adjustment for post-study treatment was partly performed for PREVAIL, this adjustment was not performed for the abiraterone data: PREVAIL started in September 2010, and the model used data up to June 2014. In the PREVAIL trial, a substantial proportion of patients received a treatment that differs from the treatment pathway currently used in the UK clinical practice. Many of the drugs PREVAIL patients are adjusted for were launched after the data threshold (May 2012) used in the model for COU-AA-302. An example is abiraterone which received FDA approval for the chemo-naïve indication in December 2012. PREVAIL patients could thus receive the drug over approximately 1.5 years. The COU-AA-302 study started in

April 2009, and data up to May 2012 was included in the model. As the trial was conducted much earlier, it is unlikely that many life extending post-study treatments were available. Also no patient level data is available for COU-AA-302 study to conduct an adjustment for treatment switching.

A limitation in the modelling of the treatment pathway is the rapidly evolving treatment landscape. A couple of years ago very limited treatment options were available for mHRPC patients, and many new treatment options are now becoming available. Due to these rapid changes it is difficult assess how a new treatment will affect the use of existing treatments in the new pathway, and what proportion of patients would receive a specific subsequent treatment.

The lack of long-term registry data on the survival of mHRPC patients is a limitation for the validation of the OS extrapolation. As no registry data was available, the extrapolation had to rely on the estimates of clinical experts.

As no resource utilisation was collected in PREVAIL, literature data was used, which was modified based on the input from UK clinical experts. Although it may be argued that using literature data introduces additional uncertainty, resource utilisation from clinical trials would also be biased due to protocol driven monitoring. To account for this, the uncertainty in cost estimates was explored in both univariate sensitivity analyses and scenario analyses.

Other limitations are the lack of EQ-5D utility data from the TAX327 trial and lack of data on the QoL impact on informal carers. Finally, a possible limitation of the June 2014 data cut-off is that no death sweep was performed for this analysis. Where the survival status is not known, the analysis conservatively assumes the date of the last visit as the censoring date. As more patients in the enzalutamide arm were still alive at the data cut-off, the lack of accurate survival data could have underestimated enzalutamide's benefit.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Head to head trials could overcome the limitations of the ITC, also a trial with a longer follow-up would reduce uncertainty regarding the extrapolation of survival curves. Also an analysis including a death sweep would reduce uncertainty. A prospective observational survey of mHRPC patients and informal carer until death would allow more accurate estimation of QoL. Also a methodological work to identify a simple, yet robust way of addressing the impact of correlated parameters like intercept and scale would help to accurately assess uncertainty in the model.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Annual prevalence of mHRPC in England and Wales in 2013 was estimated as 12,029[32]. Using 2015 population estimates[33,34], this equates to 12,172 in 2015 and to 12,642 in 2020.

Of these men, 40% are estimated to have received docetaxel chemotherapy while the remaining 60% are chemo-naïve[35]. The majority of chemo-naïve patients are asymptomatic or mildly symptomatic. In a recent US survey study involving five US comprehensive cancer centres in the Prostate Cancer Clinical Trials Consortium that incorporated the BPI, 76% (N=44/58) of patients with mHRPC who were chemo-naïve had a BPI ≤3[36]. Based on these findings, it is estimated that the number of asymptomatic or mildly symptomatic chemo-naïve mHRPC patients in England and Wales will range between 5,400 and 5,800 (Table C1).

In our estimates we assume that enzalutamide would become available at Q3 in 2015. Thus, only 25% of new cases in 2015 would be eligible for enzalutamide.

Table C1 Eligible patient population for treatment of adult men with asymptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet indicated

	2015	2016	2017	2018	2019	2020
Male population in England[33] and Wales[34]	28,480,411	28,709,686	28,931,107	29,153,465	29,368,865	29,582,107
Estimated number of new mHRPC patients[32]	12,172	12,270	12,364	12,459	12,551	12,642
Chemo-naïve[35]	7,303	7,362	7,419	7,476	7,531	7,585
Asymptomatic or mildly symptomatic patients[36]	5,446	5,585	5,628	5,671	5,713	5,755
Eligible patient population	**1,385***	**5,585**	**5,628**	**5,671**	**5,713**	**5,755**

*Based on enzalutamide being available at 2015 Q4 and thus, only 25% of all new cases being eligible for enzalutamide.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Median treatment exposure to enzalutamide in the PREVAIL study was 16.6 months. In real clinical practice patients would be treated with enzalutamide for more than one year. However, to simplify the model all treatment-associated costs are incurred in one year. No costs are carried over in the following year for enzalutamide or abiraterone (see **section 8.7**).

8.3 What assumption(s) were made about market share (when relevant)?

The market share estimates in Table C2 are based on enzalutamide receiving positive NICE guidance end of Q3 2015.

Table C2 Market share estimates for adult men with asymptomatic or mildly symptomatic mHRPC in whom chemotherapy is not yet indicated

	2015	2016	2017	2018	2019	2020
Estimated market share enzalutamide	5%	10%	20%	30%	50%	70%
Estimated market share abiraterone	95%	90%	80%	70%	50%	30%
Patients receiving treatment with enzalutamide	69	558	1,126	1,701	2,857	4,028
Patients receiving treatment with abiraterone	1,316	5,026	4,502	3,970	2,857	1,726

We assume that abiraterone is provided to chemo-naïve patients through the CDF. At time of submission of the current STA, NICE had not recommended abiraterone in the treatment of asymptomatic or minimally symptomatic mHRPC in male adults in whom chemotherapy is not yet clinically indicated.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Costs of treatment and monitoring associated with enzalutamide are discussed in section 7.5.5. Enzalutamide does not require additional LFT and cardiovascular monitoring, which are required for abiraterone4. Lower need for monitoring with enzalutamide is likely to be perceived as an advantage in hospitals and clinics; they often struggle to keep up with the high burden associated with the regular monitoring needed with most oncology drugs. The frequency of monitoring enzalutamide was estimated at once every six weeks throughout the whole treatment duration. The cost of treatment and monitoring for enzalutamide were aligned with the median treatment duration from the PREVAIL trial of 16.6 months.

No additional costs related to AEs and SREs are included. Enzalutamide is assumed to have no incremental impact on the cost of treating AEs and SREs when compared to abiraterone in chemo-naïve mHRPC adults who are asymptomatic or minimally symptomatic.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for treatment and monitoring are detailed in section 7.5.5.

8.6 Were there any estimates of resource savings? If so, what were they?

Enzalutamide requires less frequent monitoring than abiraterone (section 7.5.5), resulting in a cost saving of £143.82 per month for the first three months (every 6 weeks with enzalutamide and every 2 weeks with abiraterone) and a saving of £39.32 per month for subsequent months thereafter (monitoring needed every 6 weeks with enzalutamide and every 4 weeks with abiraterone).

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The incremental budget impact, based on the market share difference of enzalutamide when compared to abiraterone is presented in Table C3.

In addition to the assumptions listed in sections 8.2 8.3 and 8.4, the following have also been considered to calculate the budget impact:

- All patients initiate treatment with enzalutamide or abiraterone on the first day of the year
- Treatment duration is 16.6 months for enzalutamide2 and 13.8 months for abiraterone[82]
- To simplify the model, all treatment-associated costs are incurred in one year. No costs are carried over in the following year. Thus, the costs of the first year are over-estimated. For the subsequent years, costs for those patients who will continue to be treated in the following year will be offset by the costs of the patients who initiated treatment the previous year.

Table C3 The incremental budget impact difference of enzalutamide when compared to abiraterone

	2015	2016	2017	2018	2019	2020
Market Share	5%	10%	20%	30%	50%	70%
(£)	536,208	4,324,194	8,715,088	13,173,106	22,117,392	31,189,175

Note: The budget impact difference assumes a median duration of 16.6 months for enzalutamide2 and 13.8 months for abiraterone[82]. To simplify the model, the overall treatment-associated costs for a given patient are incurred in the year when the patient initiated the treatment.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The net NHS budget impact of the recommendation of enzalutamide in chemo-naive mHRPC will be much smaller than indicated by the calculations on the previous pages because many patients are already being funded for this indication via the Cancer Drugs Fund. In the most recently available data from the CDF, between October 2013 and September 2014 there were 2,729 notifications for abiraterone in chemo-naive mHRPC; and 82 for enzalutamide in September 2014.

Additionally it is highly likely that the current NHS expenditure on NICE approved post-chemo mHRPC drugs (enzalutamide and abiraterone) will reduce markedly once the drugs are routinely available for chemo-naive patients through the NHS.

Given the advanced age and frequent comorbidities mHRPC patients have, it is likely that a significant proportion of these patients require hospital transportation for monitoring visits. The fewer monitoring visits required for enzalutamide treated patients will lead to less hospital transportation. These specific costs have not been accounted for within the health economic model, or budget impact calculation as no data are available regarding the proportion of patients needing transportation. During an advisory board, clinicians informed that the abiraterone monitoring requirements place a large burden on staff resourcing. There have been occasional reports of clinics having to hire an extra nurse to carry out all monitoring obligations9. As enzalutamide does not require these additional monitoring visits, this is an opportunity for resource savings.

9 References

References are provided at the end of this document.

10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

Provided in Reference Pack –Reference 1

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched and provider used are given in Table D1.

Table D1 Databases searches and provider used

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process (via Ovid)	OvidSP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
EMBASE	OvidSP
Science Citation Index Expanded (SCI - Expanded) and Conference Proceedings Citation Index-Science (CPCI-S)	Web of Science
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library/Wiley Interscience
Health Technology Assessment Database (HTA)	Cochrane Library/Wiley Interscience
ClinicalTrials.gov	http://www.clinicaltrials.gov
International Clinical Trials Registry Platform (ICTRP)	http://apps.who.int/trialsearch/
metaRegister of Controlled Trials (mRCT)	http://www.controlled-trials.com/mrct/
NHS Economic Evaluation Database (NHS EED)	Cochrane Library/Wiley Interscience

Database / information source	Interface / URL
Health Economic Evaluation Database (HEED)	EBSCOHost
EconLit	OvidSP
Cost-effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4
National Institute for Health and Care Excellence (NICE)	http://www.nice.org.uk/
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/index.html
Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/en
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/index.html
U.S. Food and Drug Administration (FDA)	http://www.fda.gov/
European Medicines Agency (EMA)	http://www.ema.europa.eu/ema/
American Society of Clinical Oncology (ASCO) Annual Meeting and GU (ASCO-GU) Cancers Symposium	See SLR Report[46]
American Urological Association (AUA) Annual Meeting	See SLR Report[46]
European Association of Urology (EAU) Annual Congress	See SLR Report[46]
European Society for Medical Oncology (ESMO) Congress	See SLR Report[46]
European CanCer Organisation (ECCO) Congress	See SLR Report[46]
International Society for Quality of Life Research (ISOQOL) Annual Conference	See SLR Report[46]
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	See SLR Report[46]

10.2.2 The date on which the search was conducted.

Searches were conducted on:

- 02 February 2014 for American Urological Association Annual Meeting
- 20 October 2014 for Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R* and Pubmed
- 22 October 2014 for Embase, Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index- Science (CPCI-S), Cochrane Database of Systematic Reviews Issue 10 of 12, Database of Abstracts of Reviews of Effectiveness (DARE) Issue 1 of 4, July 2014, Health Technology Assessment Database (HTA) Issue 3 of 4 July 2014, Cochrane Central Register of Controlled Trials (Central) Issue 9 of 12, Sept 2014, clinicaltrials.gov
- 23 October 2014 for International Clinical Trials Registry Platform (ICTRP), metaRegister of Controlled Trials (mRCT), NHS Economic Evaluation Database (NHS EED) - Issue 3 of 4, July 2014, Health Economic Evaluations Database (HEED), EconLit, Cost-effectiveness Analysis (CEA) Registry
- 24 October 2014: NICE, Agency for Healthcare Research and Quality (AHRQ), Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Intercollegiate Guidelines Network (SIGN), U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), American Society of Clinical Oncology (ASCO) Annual Meeting and GU Cancers Symposium, European Association of Urology Annual Congress, European Society for Medical Oncology Congress, European CanCer Organisation Congress

(ECCO), International Society for Quality of Life Research (ISOQOL) Annual Conference, International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

10.2.3 The date span of the search.

No time limits were applied to any of the searches.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

A.1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP
Search date: 20/10/14
Retrieved records: 5216
Search strategy:

1	exp Prostatic Neoplasms/	98710
2	Prostatic Intraepithelial Neoplasia/	1292
3	(prostate or prostatic).ti,ab,kf.	151664
4	or/1-3	162504
5	(enzalutamide or xtandi$).ti,ab,kf.	263
6	(MDV 3100 or mdv3100).ti,ab,kf.	178
7	(915087-33-1 or 93T0T9GKNU).rn.	0
8	(abiraterone or zytiga$).ti,ab,kf.	607
9	(154229-19-3 or G819A456D0).rn.	199
10	sipuleucel$.ti,ab,kf.	348
11	(apc8015 or provenge$).ti,ab,kf.	89
12	(917381-47-6 or 8Q622VDR18).rn.	0
13	(docetaxel or taxotere$).ti,ab,kf.	9766
14	(114977-28-5 or 699121PHCA or 148408-66-6 or 15H5577CQD).rn.	7385
15	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,kf.	198
16	(444811-40-9 or RJ00KV3VTG).rn.	0
17	Flutamide/	2425

18 (flutamid$ or apimid$ or apoflutamide$ or chimax$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or fluta cell$ or fluta gry$ or fluta la pharma$ or flutacell$ or flutagry$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or oncosal$ or pmsflutamide$ or prostacur$ or prostamid$ or prostica$ or prostogenat$ or restotard$ or sch 13521 or sch13521 or sebatrol$ or tafenil$ or testac$ or testotard$).ti,ab,kf. 2911
19 (13311-84-7 or 76W6J0943E).rn. 2425
20 (bicalutamid$ or casodex$ or cosudex$ or calutide$ or ici 176334 or ici176334 or kalumid$ or lutamidal$ or raffolutil$).ti,ab,kf. 1142
21 (90357-06-5 or A0Z3NAU9DP).rn. 955
22 (nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$ or rn 23908 or rn23908 or ru 23908 or ru23908).ti,ab,kf. 244
23 (63612-50-0 or 51G6I8B902).rn. 217
24 Cyproterone/aa [Analogs & Derivatives] 694
25 Cyproterone Acetate/ 1622
26 (cyproteron$ or androcur$ or cyprostat$ or cyproterane acetate$ or nsc 81340 or nsc81340 or nsc 81430 or nsc81430 or sh 714 or sh714 or sinovir$ or virilit$).ti,ab,kf. 2752
27 (427-51-0 or 4KM2BN5JHF).rn. 1622
28 Megestrol/aa [Analogs & Derivatives] 358
29 Megestrol Acetate/ 815
30 (megestrol$ or apomegestrol$ or bdh 1296 or bdh1296 or borea or endace$ or linmegestrol$ or maygace$ or megace$ or megaplex$ or megase$ or megastrol$ or megefren$ or megejohn$ or megestat$ or megestil$ or megestranol$ or megestrinol$ or megostat$ or mergestrol$ or mestrel$ or niagestin$ or numegestrol$ or ovaban$ or ovarid$ or pallace$ or sc 10363 or sc10363).ti,ab,kf. 1889
31 (595-33-5 or TJ2M0FR8ES).rn. 815
32 Mitoxantrone/ 3883
33 (mitoxantron$ or cl 232 or cl 232315 or cl232 or cl232315 or cl 232325 or cl232325 or dhad$ or dhaq$ or domitrone$ or elsep$ or formyxan$ or misostol$ or mitoxanthron$ or mitoxgen$ or mitozantron$ or mitroxantron$ or mitroxon$ or neotalem$ or norexan$ or novanthron$ or novantron$ or now 85 34 or now85 34 or now 8534 or now8534 or nsc 279836 or nsc279836 or nsc 301739 or nsc301739 or nsc 301739d or nsc301739d or nsc 299195 or nsc299195 or nsc287836 or nsc 287836 or oncotron$ or onkotron$ or pralifan$ or ralenova$).ti,ab,kf. 4779
34 (65271-80-9 or 70476-82-3 or BZ114NVM5P or U6USW86RD0).rn. 3883
35 Prednisone/ 35427
36 (prednison$ or ancortone$ or apoprednisone$ or biocortone$ or colisone$ or cortan$ or cortidelt$ or cortiprex$ or cutason$ or dacorten$ or dacortin$ or de cortisyl$ or decortancyl$ or decortin$ or decortisyl$ or dehydrocortisone$ or dekortin$ or delitisone$ or dellacort$ or delta cortelan$ or delta cortisone$ or delta

dome$ or delta e$ or delta prenovis$ or delta sone$ or deltadome$ or deltacorten$ or deltacortisone$ or deltacortone$ or deltasone$ or deltison$ or deltra$ or di adreson$ or diadreson$ or drazone$ or encorton$ or enkorton$ or enkortolon$ or fernisone$ or hostacortin$ or insone$ or kortancyl$ or liquid pred$ or lodotra$ or me-korti$ or mekorti$ or meprison$ or metacortandracin$ or meticorten$ or meticortine$ or nisona$ or nsc 10023$ or nsc10023$ or orasone$ or orisane$ or panafcort$ or panasol$ or paracort$ or pehacort$ or precort$ or predni tablinen$ or prednicen$ or prednicorm$ or prednicot$ or prednidib$ or predniment$ or prednitone$ or pronison$ or pronizon$ or pulmison$ or rayos$ or rectodelt$ or servisone$ or sone or steerometz$ or sterapred$ or ultracorten$ or urtilone$ or winpred$).ti,ab,kf. 29788

37	(53-03-2 or VB0R961HZT).rn.	35427
38	or/5-37	77873
39	4 and 38	6259
40	editorial.pt.	373528
41	news.pt.	173549
42	case reports/	1726390
43	or/40-42	2271180
44	39 not 43	5683
45	animals/ not humans/	3983385
46	44 not 45	5216

A.2: Source: PubMed

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 20/10/14
Retrieved records: 5038
Search strategy:

#50 Search (#48 NOT #49) 5038
#49 Search animals[mh:noexp] NOT humans[mh:noexp] 3843282
#48 Search (#43 NOT #47) 5488
#47 Search (#44 OR #45 OR #46) 2216291
#46 Search "Case Reports" [Publication Type:NoExp] 1692401
#45 Search news[pt] 163755
#44 Search editorial[pt] 362309
#43 Search (#4 AND #42) 6047
#42 Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41) 75822
#41 Search (53-03-2[rn] OR VB0R961HZT[rn] OR 53-03-2[nm] OR VB0R961HZT[nm]) 34517

#40 Search (me-korti*[tiab] OR tablinen*[tiab] OR me-korti*[ot] OR tablinen*[ot]) 1

#39 Search ((delta[tiab] OR delta[ot]) AND (dome*[tiab] OR prenovis*[tiab] OR sone*[tiab] OR dome*[ot] OR prenovis*[ot] OR sone*[ot])) 331

#38 Search (delta e*[tiab] OR delta e*[ot]) 3369

#37 Search (cortisyl*[tiab] OR cortelan*[tiab] OR delta cortisone*[tiab] OR di adreson*[tiab] OR liquid pred*[tiab] OR nsc 10023*[tiab] OR cortisyl*[ot] OR cortelan*[ot] OR delta cortisone*[ot] OR di adreson*[ot] OR liquid pred*[ot] OR nsc 10023*[ot]) 179

#36 Search (prednison*[tiab] OR ancortone*[tiab] OR apoprednisone*[tiab] OR biocortone*[tiab] OR colisone*[tiab] OR cortan*[tiab] OR cortidelt*[tiab] OR cortiprex*[tiab] OR cutason*[tiab] OR dacorten*[tiab] OR dacortin*[tiab] OR decortancyl*[tiab] OR decortin*[tiab] OR decortisyl*[tiab] OR dehydrocortisone*[tiab] OR dekortin*[tiab] OR delitisone*[tiab] OR dellacort*[tiab] OR deltadome*[tiab] OR deltacorten*[tiab] OR deltacortisone*[tiab] OR deltacortone*[tiab] OR deltasone*[tiab] OR deltison*[tiab] OR deltra*[tiab] OR diadreson*[tiab] OR drazone*[tiab] OR encorton*[tiab] OR enkorton*[tiab] OR enkortolon*[tiab] OR fernisone*[tiab] OR hostacortin*[tiab] OR insone*[tiab] OR kortancyl*[tiab] OR lodotra*[tiab] OR mekorti*[tiab] OR meprison*[tiab] OR metacortandracin*[tiab] OR meticorten*[tiab] OR meticortine*[tiab] OR nisona*[tiab] OR nsc10023*[tiab] OR orasone*[tiab] OR orisane*[tiab] OR panafcort*[tiab] OR panasol*[tiab] OR paracort*[tiab] OR pehacort*[tiab] OR precort*[tiab] OR prednicen*[tiab] OR prednicorm*[tiab] OR prednicot*[tiab] OR prednidib*[tiab] OR predniment*[tiab] OR prednitone*[tiab] OR pronison*[tiab] OR pronizon*[tiab] OR pulmison*[tiab] OR rayos*[tiab] OR rectodelt*[tiab] OR servisone*[tiab] OR sone[tiab] OR steerometz*[tiab] OR sterapred*[tiab] OR ultracorten*[tiab] OR urtilone*[tiab] OR winpred*[tiab] OR prednison*[ot] OR ancortone*[ot] OR apoprednisone*[ot] OR biocortone*[ot] OR colisone*[ot] OR cortan*[ot] OR cortidelt*[ot] OR cortiprex*[ot] OR cutason*[ot] OR dacorten*[ot] OR dacortin*[ot] OR decortancyl*[ot] OR decortin*[ot] OR decortisyl*[ot] OR dehydrocortisone*[ot] OR dekortin*[ot] OR delitisone*[ot] OR dellacort*[ot] OR deltadome*[ot] OR deltacorten*[ot] OR deltacortisone*[ot] OR deltacortone*[ot] OR deltasone*[ot] OR deltison*[ot] OR deltra*[ot] OR diadreson*[ot] OR drazone*[ot] OR encorton*[ot] OR enkorton*[ot] OR enkortolon*[ot] OR fernisone*[ot] OR hostacortin*[ot] OR insone*[ot] OR kortancyl*[ot] OR lodotra*[ot] OR mekorti*[ot] OR meprison*[ot] OR metacortandracin*[ot] OR meticorten*[ot] OR meticortine*[ot] OR nisona*[ot] OR nsc10023*[ot] OR orasone*[ot] OR orisane*[ot] OR panafcort*[ot] OR panasol*[ot] OR paracort*[ot] OR pehacort*[ot] OR precort*[ot] OR prednicen*[ot] OR prednicorm*[ot] OR prednicot*[ot] OR prednidib*[ot] OR predniment*[ot] OR prednitone*[ot] OR pronison*[ot] OR pronizon*[ot] OR pulmison*[ot] OR rayos*[ot] OR rectodelt*[ot] OR servisone*[ot] OR sone[ot] OR steerometz*[ot] OR sterapred*[ot] OR ultracorten*[ot] OR urtilone*[ot] OR winpred*[ot]) 25078

#35 Search "Prednisone"[Mesh:NoExp] 34517

#34 Search (65271-80-9[rn] OR 70476-82-3[rn] OR BZ114NVM5P[rn] OR U6USW86RD0[rn] OR 65271-80-9[nm] OR 70476-82-3[nm] OR BZ114NVM5P[nm] OR U6USW86RD0[nm]) 3784

#33 Search (mitoxantron*[tiab] OR cl 232[tiab] OR cl 232315[tiab] OR cl232[tiab] OR cl232315[tiab] OR cl 232325[tiab] OR cl232325[tiab] OR dhad*[tiab] OR dhaq*[tiab] OR domitrone*[tiab] OR elsep*[tiab] OR formyxan*[tiab] OR misostol*[tiab] OR mitoxanthron*[tiab] OR mitoxgen*[tiab] OR mitozantron*[tiab] OR mitroxantron*[tiab] OR mitroxon*[tiab] OR neotalem*[tiab] OR norexan*[tiab] OR novanthron*[tiab] OR novantron*[tiab] OR now 85 34[tiab] OR now85 34[tiab] OR now 8534[tiab] OR now8534[tiab] OR nsc 279836[tiab] OR nsc279836[tiab] OR nsc 301739[tiab] OR nsc301739[tiab] OR nsc 301739d[tiab] OR nsc301739d[tiab] OR nsc 299195[tiab] OR nsc299195[tiab] OR nsc287836[tiab] OR nsc 287836[tiab] OR oncotron*[tiab] OR onkotron*[tiab] OR pralifan*[tiab] OR ralenova*[tiab] OR mitoxantron*[ot] OR cl 232[ot] OR cl 232315[ot] OR cl232[ot] OR cl232315[ot] OR cl 232325[ot] OR cl232325[ot] OR dhad*[ot] OR dhaq*[ot] OR domitrone*[ot] OR elsep*[ot] OR formyxan*[ot] OR misostol*[ot] OR mitoxanthron*[ot] OR mitoxgen*[ot] OR mitozantron*[ot] OR mitroxantron*[ot] OR mitroxon*[ot] OR neotalem*[ot] OR norexan*[ot] OR novanthron*[ot] OR novantron*[ot] OR now 85 34[ot] OR now85 34[ot] OR now 8534[ot] OR now8534[ot] OR nsc 279836[ot] OR nsc279836[ot] OR nsc 301739[ot] OR nsc301739[ot] OR nsc 301739d[ot] OR nsc301739d[ot] OR nsc 299195[ot] OR nsc299195[ot] OR nsc287836[ot] OR nsc 287836[ot] OR oncotron*[ot] OR onkotron*[ot] OR pralifan*[ot] OR ralenova*[ot]) 4708
#32 Search "Mitoxantrone"[Mesh:NoExp] 3784
#31 Search (595-33-5[rn] OR TJ2M0FR8ES[rn] OR 595-33-5[nm] OR TJ2M0FR8ES[nm]) 794
#30 Search (megestrol*[tiab] OR apomegestrol*[tiab] OR bdh 1296[tiab] OR bdh1296[tiab] OR borea[tiab] OR endace*[tiab] OR linmegestrol*[tiab] OR maygace*[tiab] OR megace*[tiab] OR megaplex*[tiab] OR megase*[tiab] OR megastrol*[tiab] OR megefren*[tiab] OR megejohn*[tiab] OR megestat*[tiab] OR megestil*[tiab] OR megestranol*[tiab] OR megestrinol*[tiab] OR megostat*[tiab] OR mergestrol*[tiab] OR mestrel*[tiab] OR niagestin*[tiab] OR numegestrol*[tiab] OR ovaban*[tiab] OR ovarid*[tiab] OR pallace*[tiab] OR sc 10363[tiab] OR sc10363[tiab] OR megestrol*[ot] OR apomegestrol*[ot] OR bdh 1296[ot] OR bdh1296[ot] OR borea[ot] OR endace*[ot] OR linmegestrol*[ot] OR maygace*[ot] OR megace*[ot] OR megaplex*[ot] OR megase*[ot] OR megastrol*[ot] OR megefren*[ot] OR megejohn*[ot] OR megestat*[ot] OR megestil*[ot] OR megestranol*[ot] OR megestrinol*[ot] OR megostat*[ot] OR mergestrol*[ot] OR mestrel*[ot] OR niagestin*[ot] OR numegestrol*[ot] OR ovaban*[ot] OR ovarid*[ot] OR pallace*[ot] OR sc 10363[ot] OR sc10363[ot]) 1870
#29 Search "Megestrol Acetate"[Mesh:NoExp] 794
#28 Search "Megestrol/analogs and derivatives"[Mesh:NoExp] 354
#27 Search (427-51-0[rn] OR 4KM2BN5JHF[rn] OR 427-51-0[nm] OR 4KM2BN5JHF[nm]) 1597
#26 Search (cyproteron*[tiab] OR androcur*[tiab] OR cyprostat*[tiab] OR cyproterane[tiab] OR nsc 81340[tiab] OR nsc81340[tiab] OR nsc 81430[tiab] OR nsc81430[tiab] OR sh 714[tiab] OR sh714[tiab] OR sinovir*[tiab] OR virilit*[tiab] OR cyproteron*[ot] OR androcur*[ot] OR cyprostat*[ot] OR cyproterane[ot] OR nsc

81340[ot] OR nsc81340[ot] OR nsc 81430[ot] OR nsc81430[ot] OR sh 714[ot] OR sh714[ot] OR sinovir*[ot] OR virilit*[ot]) 2730
#25 Search "Cyproterone Acetate"[Mesh:NoExp] 1597
#24 Search "Cyproterone/analogs and derivatives"[Mesh:NoExp] 685
#23 Search (63612-50-0[rn] OR 51G6I8B902[rn] OR 63612-50-0[nm] OR 51G6I8B902[nm]) 214
#22 Search (nilutamid*[tiab] OR anadron*[tiab] OR anandron*[tiab] OR canandron*[tiab] OR nilandron*[tiab] OR nitulamide*[tiab] OR rn 23908[tiab] OR rn23908[tiab] OR ru 23908[tiab] OR ru23908[tiab] OR nilutamid*[ot] OR anadron*[ot] OR anandron*[ot] OR canandron*[ot] OR nilandron*[ot] OR nitulamide*[ot] OR rn 23908[ot] OR rn23908[ot] OR ru 23908[ot] OR ru23908[ot])252
#21 Search (90357-06-5[rn] OR A0Z3NAU9DP[rn] OR 90357-06-5[nm] OR A0Z3NAU9DP[nm]) 894
#20 Search (bicalutamid*[tiab] OR casodex*[tiab] OR cosudex*[tiab] OR calutide*[tiab] OR ici 176334[tiab] OR ici176334[tiab] OR kalumid*[tiab] OR lutamidal*[tiab] OR raffolutil*[tiab] OR bicalutamid*[ot] OR casodex*[ot] OR cosudex*[ot] OR calutide*[ot] OR ici 176334[ot] OR ici176334[ot] OR kalumid*[ot] OR lutamidal*[ot] OR raffolutil*[ot]) 1096
#19 Search (13311-84-7[rn] OR 76W6J0943E[rn] OR 13311-84-7[nm] OR 76W6J0943E[nm]) 2353
#18 Search (fluta[tiab] AND (cell*[tiab] OR gry*[tiab] OR pharma*[tiab])) OR (fluta[ot] AND (cell*[ot] OR gry*[ot] OR pharma*[ot])) 1
#17 Search sch 13521[tiab] OR sch 13521[ot] 22
#16 Search (flutamid*[ot] OR apimid*[ot] OR apoflutamide*[ot] OR chimax*[ot] OR cytamid*[ot] OR drogenil*[ot] OR etaconil*[ot] OR euflex*[ot] OR eulexin*[ot] OR flucinom*[ot] OR fludinom*[ot] OR flugerel*[ot] OR fluken*[ot] OR flulem*[ot] OR flumid*[ot] OR flutacell*[ot] OR flutagry*[ot] OR flutamex*[ot] OR flutamin*[ot] OR flutan*[ot] OR flutaplex*[ot] OR flutax*[ot] OR flutexin*[ot] OR flutol*[ot] OR fluxus*[ot] OR fugerel*[ot] OR grisetin*[ot] OR niftolid*[ot] OR niphtholid*[ot] OR novoflutamide*[ot] OR odyne*[ot] OR oncosal*[ot] OR pmsflutamide*[ot] OR prostacur*[ot] OR prostamid*[ot] OR prostica*[ot] OR prostogenat*[ot] OR restotard*[ot] OR sch13521[ot] OR sebatrol*[ot] OR tafenil*[ot] OR testac*[ot] OR testotard*[ot]) 40
#15 Search (flutamid*[tiab] OR apimid*[tiab] OR apoflutamide*[tiab] OR chimax*[tiab] OR cytamid*[tiab] OR drogenil*[tiab] OR etaconil*[tiab] OR euflex*[tiab] OR eulexin*[tiab] OR flucinom*[tiab] OR fludinom*[tiab] OR flugerel*[tiab] OR fluken*[tiab] OR flulem*[tiab] OR flumid*[tiab] OR flutacell*[tiab] OR flutagry*[tiab] OR flutamex*[tiab] OR flutamin*[tiab] OR flutan*[tiab] OR flutaplex*[tiab] OR flutax*[tiab] OR flutexin*[tiab] OR flutol*[tiab] OR fluxus*[tiab] OR fugerel*[tiab] OR grisetin*[tiab] OR niftolid*[tiab] OR niphtholid*[tiab] OR novoflutamide*[tiab] OR odyne*[tiab] OR oncosal*[tiab] OR pmsflutamide*[tiab] OR prostacur*[tiab] OR prostamid*[tiab] OR prostica*[tiab] OR prostogenat*[tiab] OR restotard*[tiab] OR sch13521[tiab] OR sebatrol*[tiab] OR tafenil*[tiab] OR testac*[tiab] OR testotard*[tiab]) 2835
#14 Search "Flutamide"[Mesh:NoExp] 2353

#13 Search (radium-223[tiab] OR ra223[tiab] OR ra-223[tiab] OR xofigo*[tiab] OR alpharadin*[tiab] OR radium-223[ot] OR ra223[ot] OR ra-223[ot] OR xofigo*[ot] OR alpharadin*[ot] OR 444811-40-9[rn] OR RJ00KV3VTG[rn] OR 444811-40-9[nm] OR RJ00KV3VTG[nm]) 186
#12 Search (114977-28-5[rn] OR 699121PHCA[rn] OR 148408-66-6[rn] OR 15H5577CQD[rn] OR 114977-28-5[nm] OR 699121PHCA[nm] OR 148408-66-6[nm] OR 15H5577CQD[nm]) 7021
#11 Search (docetaxel[tiab] OR taxotere*[tiab] OR docetaxel[ot] OR taxotere*[ot]) 9603
#10 Search (apc8015[tiab] OR provenge*[tiab] OR apc8015[ot] OR provenge*[ot] OR 917381-47-6[rn] OR 8Q622VDR18[rn] OR 917381-47-6[nm] OR 8Q622VDR18[nm]) 92
#9 Search (sipuleucel*[tiab] OR sipuleucel*[ot]) 336
#8 Search (154229-19-3[rn] OR G819A456D0[rn] OR 154229-19-3[nm] OR G819A456D0[nm]) 166
#7 Search (abiraterone[tiab] OR zytiga*[tiab] OR abiraterone[ot] OR zytiga*[ot]) 578
#6 Search (MDV 3100[tiab] OR mdv3100[tiab] OR MDV 3100[ot] OR mdv3100[ot] OR 915087-33-1[rn] OR 93T0T9GKNU[rn] OR 915087-33-1[nm] OR 93T0T9GKNU[nm]) 158
#5 Search (enzalutamide[tiab] OR xtandi*[tiab] OR enzalutamide[ot] OR xtandi*[ot]) 277
#4 Search (#1 OR #2 OR #3) 157818
#3 Search (prostate[tiab] OR prostatic[tiab] OR prostate[ot] OR prostatic[ot]) 147440
#2 Search "Prostatic Intraepithelial Neoplasia"[Mesh] 1192
#1 Search "Prostatic Neoplasms"[Mesh] 92704

A.3: Source: Embase 1974 to 2014 October 21

Interface / URL: OvidSP
Search date: 22/10/14
Retrieved records: 5569
Search strategy:

1 exp prostate tumor/ 159267
2 (prostate or prostatic).ti,ab,kw. 192118
3 or/1-2 222461
4 enzalutamide/ 841
5 (enzalutamide or xtandi$).ti,ab,kw. 436
6 (MDV 3100 or mdv3100).ti,ab,kw. 303
7 915087-33-1.rn. 802
8 or/4-7 1168
9 abiraterone/ 1041
10 abiraterone acetate/ 995

11 (abiraterone or zytiga$).ti,ab,kw. 1141
12 154229-19-3.rn. 756
13 sipuleucel T/ 870
14 sipuleucel$.ti,ab,kw. 528
15 (apc8015 or provenge$).ti,ab,kw. 137
16 917381-47-6.rn. 690
17 docetaxel/ 35831
18 (docetaxel or taxotere$).ti,ab,kw. 15820
19 (114977-28-5 or 148408-66-6).rn. 31020
20 radium chloride ra 223/ 262
21 (radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,kw. 309
22 444811-40-9.rn. 0
23 flutamide/ 7053
24 (flutamid$ or apimid$ or apoflutamide$ or chimax$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or fluta cell$ or fluta gry$ or fluta la pharma$ or flutacell$ or flutagry$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or oncosal$ or pmsflutamide$ or prostacur$ or prostamid$ or prostica$ or prostogenat$ or restotard$ or sch 13521 or sch13521 or sebatrol$ or tafenil$ or testac$ or testotard$).ti,ab,kw. 3451
25 13311-84-7.rn. 6835
26 bicalutamide/ 4278
27 (bicalutamid$ or casodex$ or cosudex$ or calutide$ or ici 176334 or ici176334 or kalumid$ or lutamidal$ or raffolutil$).ti,ab,kw. 1630
28 90357-06-5.rn. 3876
29 nilutamide/ 1257
30 (nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$ or rn 23908 or rn23908 or ru 23908 or ru23908).ti,ab,kw. 293
31 63612-50-0.rn. 1242
32 cyproterone acetate/ 6914
33 (cyproteron$ or androcur$ or cyprostat$ or cyproterane acetate$ or nsc 81340 or nsc81340 or nsc 81430 or nsc81430 or sh 714 or sh714 or sinovir$ or virilit$).ti,ab,kw. 3329
34 427-51-0.rn. 6824
35 megestrol acetate/ 4430
36 (megestrol$ or apomegestrol$ or bdh 1296 or bdh1296 or borea or endace$ or linmegestrol$ or maygace$ or megace$ or megaplex$ or megase$ or megastrol$ or megefren$ or megejohn$ or megestat$ or megestil$ or megestranol$ or megestrinol$ or megostat$ or mergestrol$ or mestrel$ or niagestin$ or numegestrol$ or ovaban$ or ovarid$ or pallace$ or sc 10363 or sc10363).ti,ab,kw. 2184
37 595-33-5.rn. 4143
38 Mitoxantrone/ 19206
39 (mitoxantron$ or cl 232 or cl 232315 or cl232 or cl232315 or cl 232325 or cl232325 or dhad$ or dhaq$ or domitrone$ or elsep$ or formyxan$ or misostol$ or

mitoxanthron$ or mitoxgen$ or mitozantron$ or mitroxantron$ or mitroxon$ or neotalem$ or norexan$ or novanthron$ or novantron$ or now 85 34 or now85 34 or now 8534 or now8534 or nsc 279836 or nsc279836 or nsc 301739 or nsc301739 or nsc 301739d or nsc301739d or nsc 299195 or nsc299195 or nsc287836 or nsc 287836 or oncotron$ or onkotron$ or pralifan$ or ralenova$).ti,ab,kw. 6149

40 (65271-80-9 or 70476-82-3).rn. 18349

41 prednisone/ 135415

42 (prednison$ or ancortone$ or apoprednisone$ or biocortone$ or colisone$ or cortan$ or cortidelt$ or cortiprex$ or cutason$ or dacorten$ or dacortin$ or de cortisyl$ or decortancyl$ or decortin$ or decortisyl$ or dehydrocortisone$ or dekortin$ or delitisone$ or dellacort$ or delta cortelan$ or delta cortisone$ or delta dome$ or delta e$ or delta prenovis$ or delta sone$ or deltadome$ or deltacorten$ or deltacortisone$ or deltacortone$ or deltasone$ or deltison$ or deltra$ or di adreson$ or diadreson$ or drazone$ or encorton$ or enkorton$ or enkortolon$ or fernisone$ or hostacortin$ or insone$ or kortancyl$ or liquid pred$ or lodotra$ or me-korti$ or mekorti$ or meprison$ or metacortandracin$ or meticorten$ or meticortine$ or nisona$ or nsc 10023$ or nsc10023$ or orasone$ or orisane$ or panafcort$ or panasol$ or paracort$ or pehacort$ or precort$ or predni tablinen$ or prednicen$ or prednicorm$ or prednicot$ or prednidib$ or predniment$ or prednitone$ or pronison$ or pronizon$ or pulmison$ or rayos$ or rectodelt$ or servisone$ or sone or steerometz$ or sterapred$ or ultracorten$ or urtilone$ or winpred$).ti,ab,kw. 34944

43 53-03-2.rn. 128164

44 or/9-43 212909

45 3 and 8 1121

46 3 and 44 15973

47 randomized controlled trial/ 354061

48 "randomized controlled trial (topic)"/ 59605

49 crossover procedure/ 40414

50 double blind procedure/ 118276

51 single blind procedure/ 18925

52 random$.ti,ab. 919694

53 factorial$.ti,ab. 24042

54 (crossover$ or cross-over$).ti,ab. 72583

55 placebo$.ti,ab. 208628

56 doubl$ blind$.ti,ab. 150608

57 singl$ blind$.ti,ab. 15012

58 assign$.ti,ab. 247831

59 allocat$.ti,ab. 87442

60 volunteer$.ti,ab. 184945

61 trial.ti,ab. 489659

62 groups.ab. 1779472

63 or/47-62 3063269

64 "health care cost"/ 132307

65 "cost"/ 52435

66 (cost or costs or costing or burden).ti,ab. 543426
67 resource$1.ti,ab. 228242
68 ((economic or human or humanistic) adj3 consequence$1).ti,ab. 4997
69 exp economic evaluation/ 216587
70 (economic evaluation$1 or pharmacoeconomic$1).ti,ab. 14400
71 (hospitalization$1 or hospitalisation$1).ti,ab. 141531
72 (admission$1 or readmission$1 or admitted or readmitted or visit or visits).ti,ab. 513236
73 (bed adj2 days).ti,ab. 2537
74 hospital stay$1.ti,ab. 74518
75 ((days or time or length or duration$1) adj3 hospital$).ti,ab. 79033
76 ((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab. 86687
77 ((days or time or length or duration$1) adj3 (discharge or home)).ti,ab. 17597
78 (staff or staffing or personnel).ti,ab. 203157
79 or/64-78 1655444
80 63 or 79 4357946
81 46 and 80 5036
82 45 or 81 5780
83 editorial.pt. 457904
84 case report.ti. 204686
85 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ 5012148
86 83 or 84 or 85 5661187
87 82 not 86 5569

A.4: Source: Science Citation Index Expanded (SCI-EXPANDED) - 1900-present and Conference Proceedings Citation Index-Science (CPCI-S) - 1990-present

Interface / URL: Web of Science
Search date: 22/10/14
Retrieved records: 7242
Search strategy:

Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

20 7,242 #17 not (#18 or #19)
19 121,826 TI=("case report")
18 2,614,247 TI=("rat" or "rats" or "rodent" or "rodents" or "mouse" or "mice" or "murine" or "hamster" or "hamsters" or "gerbil" or "gerbils" or "animal" or "animals" or "dogs" or "dog" or "canine" or "pig" or "pigs" or "cats" or "bovine" or "cow" or "cows" or "cattle" or "sheep" or "horse" or "horses" or "equine" or "ovine" or "porcine"

or "monkey" or "monkeys" or "primate" or "primates" or "rhesus macaque" or "rhesus macaques" or "rabbit" or "rabbits")
17 7,653 #1 and #16
16 78,963 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
15 46,548 TS=(prednison* or ancortone* or apoprednisone* or biocortone* or colisone* or cortan* or cortidelt* or cortiprex* or cutason* or dacorten* or dacortin* or "de cortisyl*" or decortancyl* or decortin* or decortisyl* or dehydrocortisone* or dekortin* or delitisone* or dellacort* or "delta cortelan*" or "delta cortisone*" or "delta dome*" or "delta e*" or "delta prenovis*" or "delta sone*" or deltadome* or deltacorten* or deltacortisone* or deltacortone* or deltasone* or deltison* or deltra* or "di adreson*" or diadreson* or drazone* or encorton* or enkorton* or enkortolon* or fernisone* or hostacortin* or insone* or kortancyl* or "liquid pred*" or lodotra* or "me-korti*" or mekorti* or meprison* or metacortandracin* or meticorten* or meticortine* or nisona* or "nsc 10023*" or nsc10023* or orasone* or orisane* or panafcort* or panasol* or paracort* or pehacort* or precort* or "predni tablinen*" or prednicen* or prednicorm* or prednicot* or prednidib* or predniment* or prednitone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servisone* or sone or steerometz* or sterapred* or ultracorten* or urtilone* or winpred*)
14 7,353 TS=(mitoxantron* or "cl 232" or "cl 232315" or "cl232" or "cl232315" or "cl 232325" or "cl232325" or dhad* or dhaq* or domitrone* or elsep* or formyxan* or misostol* or mitoxanthron* or mitoxgen* or mitozantron* or mitroxantron* or mitroxon* or neotalem* or norexan* or novanthron* or novantron* or "now 85 34" or "now85 34" or "now 8534" or "now8534" or "nsc 279836" or "nsc279836" or "nsc 301739" or "nsc301739" or "nsc 301739d" or "nsc301739d" or "nsc 299195" or "nsc299195" or "nsc287836" or "nsc 287836" or oncotron* or onkotron* or pralifan* or ralenova*)
13 3,622 TS=(megestrol* or apomegestrol* or "bdh 1296" or "bdh1296" or "borea" or endace* or linmegestrol* or maygace* or megace* or megaplex* or megase* or megastrol* or megefren* or megejohn* or megestat* or megestil* or megestranol* or megestrinol* or megostat* or mergestrol* or mestrel* or niagestin* or numegestrol* or ovaban* or ovarid* or pallace* or "sc 10363" or "sc10363")
12 2,942 TS=(cyproteron* or androcur* or cyprostat* or "cyproterane acetate*" or "nsc 81340" or "nsc81340" or "nsc 81430" or "nsc81430" or "sh 714" or "sh714" or sinovir* or virilit*)
11 273 TS=(nilutamid* or anadron* or anandron* or canandron* or nilandron* or nitulamide* or "rn 23908" or "rn23908" or "ru 23908" or "ru23908")
10 1,434 TS=(bicalutamid* or casodex* or cosudex* or calutide* or "ici 176334" or "ici176334" or kalumid* or lutamidal* or raffolutil*)
9 4,359 TS=(flutamid* or apimid* or apoflutamide* or chimax* or cytamid* or drogenil* or etaconil* or euflex* or eulexin* or flucinom* or fludinom* or flugerel* or fluken* or flulem* or flumid* or "fluta cell*" or "fluta gry*" or "fluta la pharma*" or flutacell* or flutagry* or flutamex* or flutamin* or flutan* or flutaplex* or flutax* or flutexin* or flutol* or fluxus* or fugerel* or grisetin* or niftolid* or niphtholid* or novoflutamide* or odyne* or oncosal* or pmsflutamide* or prostacur* or prostamid* or

prostica* or prostogenat* or restotard* or "sch 13521" or "sch13521" or sebatrol* or tafenil* or testac* or testotard*)
8 519 TS=("radium-223" or "ra223" or "ra-223" or xofigo* or alpharadin*)
7 15,252 TS=("docetaxel" or taxotere*)
6 97 TS=("apc8015" or provenge*)
5 459 TS=(sipuleucel*)
4 942 TS=("abiraterone" or zytiga*)
3 191 TS=("mdv 3100" or "mdv3100")
2 282 TS=("enzalutamide" or xtandi*)
1 197,487 TS=("prostate" or "prostatic")

A.5: Source: Cochrane Database of Systematic Reviews Issue 10 of 12, October 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 22/10/14
Retrieved records: 65
Search strategy:

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3404
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 32
#3 (prostate or prostatic) 10487
#4 {or #1-#3} 10487
#5 (enzalutamide or xtandi*) 13
#6 ("MDV 3100" or mdv3100) 4
#7 (abiraterone or zytiga*) 34
#8 sipuleucel* 26
#9 (apc8015 or provenge*) 17
#10 (docetaxel or taxotere*) 2210
#11 (radium-223 or ra223 or ra-223 or xofigo* or alpharadin*) 16
#12 MeSH descriptor: [Flutamide] this term only 281
#13 (flutamid* or apimid* or apoflutamide* or chimax* or cytamid* or drogenil* or etaconil* or euflex* or eulexin* or flucinom* or fludinom* or flugerel* or fluken* or flulem* or flumid* or fluta next cell* or fluta next gry* or fluta next la next pharma* or flutacell* or flutagry* or flutamex* or flutamin* or flutan* or flutaplex* or flutax* or flutexin* or flutol* or fluxus* or fugerel* or grisetin* or niftolid* or niphtholid* or novoflutamide* or odyne* or oncosal* or pmsflutamide* or prostacur* or prostamid* or prostica* or prostogenat* or restotard* or "sch 13521" or sch13521 or sebatrol* or tafenil* or testac* or testotard*) 457
#14 (bicalutamid* or casodex* or cosudex* or calutide* or "ici 176334" or ici176334 or kalumid* or lutamidal* or raffolutil*) 203
#15 (nilutamid* or anadron* or anandron* or canandron* or nilandron* or nitulamide* or "rn 23908" or rn23908 or "ru 23908" or ru23908) 58

#16 MeSH descriptor: [Cyproterone] this term only and with qualifier(s): [Analogs & derivatives - AA] 66
#17 MeSH descriptor: [Cyproterone Acetate] this term only 255
#18 (cyproteron* or androcur* or cyprostat* or cyproterane next acetate* or "nsc 81340" or nsc81340 or "nsc 81430" or nsc81430 or "sh 714" or sh714 or sinovir* or virilit*) 499
#19 MeSH descriptor: [Megestrol] this term only and with qualifier(s): [Analogs & derivatives - AA] 68
#20 MeSH descriptor: [Megestrol Acetate] this term only 159
#21 (megestrol* or apomegestrol* or "bdh 1296" or bdh1296 or borea or endace* or linmegestrol* or maygace* or megace* or megaplex* or megase* or megastrol* or megefren* or megejohn* or megestat* or megestil* or megestranol* or megestrinol* or megostat* or mergestrol* or mestrel* or niagestin* or numegestrol* or ovaban* or ovarid* or pallace* or "sc 10363" or sc10363) 502
#22 MeSH descriptor: [Mitoxantrone] this term only 375
#23 (mitoxantron* or "cl 232" or "cl 232315" or cl232 or cl232315 or "cl 232325" or cl232325 or dhad* or dhaq* or domitrone* or elsep* or formyxan* or misostol* or mitoxanthron* or mitoxgen* or mitozantron* or mitroxantron* or mitroxon* or neotalem* or norexan* or novanthron* or novantron* or "now 85 34" or "now85 34" or "now 8534" or now8534 or "nsc 279836" or nsc279836 or "nsc 301739" or nsc301739 or "nsc 301739d" or nsc301739d or "nsc 299195" or nsc299195 or nsc287836 or "nsc 287836" or oncotron* or onkotron* or pralifan* or ralenova*) 1008
#24 MeSH descriptor: [Prednisone] this term only 2837
#25 (prednison* or ancortone* or apoprednisone* or biocortone* or colisone* or cortan* or cortidelt* or cortiprex* or cutason* or dacorten* or dacortin* or de next cortisyl* or decortancyl* or decortin* or decortisyl* or dehydrocortisone* or dekortin* or delitisone* or dellacort* or delta next cortelan* or delta next cortisone* or delta next dome* or delta next e* or delta next prenovis* or delta next sone* or deltadome* or deltacorten* or deltacortisone* or deltacortone* or deltasone* or deltison* or deltra* or di next adreson* or diadreson* or drazone* or encorton* or enkorton* or enkortolon* or fernisone* or hostacortin* or insone* or kortancyl* or liquid next pred* or lodotra* or me-korti* or mekorti* or meprison* or metacortandracin* or meticorten* or meticortine* or nisona* or nsc next 10023* or nsc10023* or orasone* or orisane* or panafcort* or panasol* or paracort* or pehacort* or precort* or predni next tablinen* or prednicen* or prednicorm* or prednicot* or prednidib* or predniment* or prednitone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servisone* or sone or steerometz* or sterapred* or ultracorten* or urtilone* or winpred*) 8920
#26 (1-#25) 13393
#27 #4 and #26 in Cochrane Reviews (Reviews and Protocols) 65

A.6: Source: Database of Abstracts of Reviews of Effectiveness (DARE) Issue 1 of 4, July 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 22/10/14
Retrieved records: 21
Search strategy:

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3404
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 32
#3 (prostate or prostatic) 10487
#4 {or #1-#3} 10487
#5 (enzalutamide or xtandi*) 13
#6 ("MDV 3100" or mdv3100) 4
#7 (abiraterone or zytiga*) 34
#8 sipuleucel* 26
#9 (apc8015 or provenge*) 17
#10 (docetaxel or taxotere*) 2210
#11 (radium-223 or ra223 or ra-223 or xofigo* or alpharadin*) 16
#12 MeSH descriptor: [Flutamide] this term only 281
#13 (flutamid* or apimid* or apoflutamide* or chimax* or cytamid* or drogenil* or etaconil* or euflex* or eulexin* or flucinom* or fludinom* or flugerel* or fluken* or flulem* or flumid* or fluta next cell* or fluta next gry* or fluta next la next pharma* or flutacell* or flutagry* or flutamex* or flutamin* or flutan* or flutaplex* or flutax* or flutexin* or flutol* or fluxus* or fugerel* or grisetin* or niftolid* or niphtholid* or novoflutamide* or odyne* or oncosal* or pmsflutamide* or prostacur* or prostamid* or prostica* or prostogenat* or restotard* or "sch 13521" or sch13521 or sebatrol* or tafenil* or testac* or testotard*) 457
#14 (bicalutamid* or casodex* or cosudex* or calutide* or "ici 176334" or ici176334 or kalumid* or lutamidal* or raffolutil*) 203
#15 (nilutamid* or anadron* or anandron* or canandron* or nilandron* or nitulamide* or "rn 23908" or rn23908 or "ru 23908" or ru23908) 58
#16 MeSH descriptor: [Cyproterone] this term only and with qualifier(s): [Analogs & derivatives - AA] 66
#17 MeSH descriptor: [Cyproterone Acetate] this term only 255
#18 (cyproteron* or androcur* or cyprostat* or cyproterane next acetate* or "nsc 81340" or nsc81340 or "nsc 81430" or nsc81430 or "sh 714" or sh714 or sinovir* or virilit*) 499
#19 MeSH descriptor: [Megestrol] this term only and with qualifier(s): [Analogs & derivatives - AA] 68
#20 MeSH descriptor: [Megestrol Acetate] this term only 159
#21 (megestrol* or apomegestrol* or "bdh 1296" or bdh1296 or borea or endace* or linmegestrol* or maygace* or megace* or megaplex* or megase* or megastrol* or megefren* or megejohn* or megestat* or megestil* or megestranol* or megestrinol* or megostat* or mergestrol* or mestrel* or niagestin* or numegestrol* or ovaban* or ovarid* or pallace* or "sc 10363" or sc10363) 502
#22 MeSH descriptor: [Mitoxantrone] this term only 375

#23 (mitoxantron* or "cl 232" or "cl 232315" or cl232 or cl232315 or "cl 232325" or cl232325 or dhad* or dhaq* or domitrone* or elsep* or formyxan* or misostol* or mitoxanthron* or mitoxgen* or mitozantron* or mitroxantron* or mitroxon* or neotalem* or norexan* or novanthron* or novantron* or "now 85 34" or "now85 34" or "now 8534" or now8534 or "nsc 279836" or nsc279836 or "nsc 301739" or nsc301739 or "nsc 301739d" or nsc301739d or "nsc 299195" or nsc299195 or nsc287836 or "nsc 287836" or oncotron* or onkotron* or pralifan* or ralenova*) 1008
#24 MeSH descriptor: [Prednisone] this term only 2837
#25 (prednison* or ancortone* or apoprednisone* or biocortone* or colisone* or cortan* or cortidelt* or cortiprex* or cutason* or dacorten* or dacortin* or de next cortisyl* or decortancyl* or decortin* or decortisyl* or dehydrocortisone* or dekortin* or delitisone* or dellacort* or delta next cortelan* or delta next cortisone* or delta next dome* or delta next e* or delta next prenovis* or delta next sone* or deltadome* or deltacorten* or deltacortisone* or deltacortone* or deltasone* or deltison* or deltra* or di next adreson* or diadreson* or drazone* or encorton* or enkorton* or enkortolon* or fernisone* or hostacortin* or insone* or kortancyl* or liquid next pred* or lodotra* or me-korti* or mekorti* or meprison* or metacortandracin* or meticorten* or meticortine* or nisona* or nsc next 10023* or nsc10023* or orasone* or orisane* or panafcort* or panasol* or paracort* or pehacort* or precort* or predni next tablinen* or prednicen* or prednicorm* or prednicot* or prednidib* or predniment* or prednitone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servisone* or sone or steerometz* or sterapred* or ultracorten* or urtilone* or winpred*) 8920
#26 (1-#25) 13393
#27 #4 and #26 in Other Reviews 21

A.7: Source: Health Technology Assessment Database (HTA) Issue 3 of 4 July 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 22/10/14
Retrieved records: 36
Search strategy:

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3404
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 32
#3 (prostate or prostatic) 10487
#4 {or #1-#3} 10487
#5 (enzalutamide or xtandi*) 13
#6 ("MDV 3100" or mdv3100) 4
#7 (abiraterone or zytiga*) 34
#8 sipuleucel* 26
#9 (apc8015 or provenge*) 17
#10 (docetaxel or taxotere*) 2210

#11 (radium-223 or ra223 or ra-223 or xofigo* or alpharadin*) 16
#12 MeSH descriptor: [Flutamide] this term only 281
#13 (flutamid* or apimid* or apoflutamide* or chimax* or cytamid* or drogenil* or etaconil* or euflex* or eulexin* or flucinom* or fludinom* or flugerel* or fluken* or flulem* or flumid* or fluta next cell* or fluta next gry* or fluta next la next pharma* or flutacell* or flutagry* or flutamex* or flutamin* or flutan* or flutaplex* or flutax* or flutexin* or flutol* or fluxus* or fugerel* or grisetin* or niftolid* or niphtholid* or novoflutamide* or odyne* or oncosal* or pmsflutamide* or prostacur* or prostamid* or prostica* or prostogenat* or restotard* or "sch 13521" or sch13521 or sebatrol* or tafenil* or testac* or testotard*) 457
#14 (bicalutamid* or casodex* or cosudex* or calutide* or "ici 176334" or ici176334 or kalumid* or lutamidal* or raffolutil*) 203
#15 (nilutamid* or anadron* or anandron* or canandron* or nilandron* or nitulamide* or "rn 23908" or rn23908 or "ru 23908" or ru23908) 58
#16 MeSH descriptor: [Cyproterone] this term only and with qualifier(s): [Analogs & derivatives - AA] 66
#17 MeSH descriptor: [Cyproterone Acetate] this term only 255
#18 (cyproteron* or androcur* or cyprostat* or cyproterane next acetate* or "nsc 81340" or nsc81340 or "nsc 81430" or nsc81430 or "sh 714" or sh714 or sinovir* or virilit*) 499
#19 MeSH descriptor: [Megestrol] this term only and with qualifier(s): [Analogs & derivatives - AA] 68
#20 MeSH descriptor: [Megestrol Acetate] this term only 159
#21 (megestrol* or apomegestrol* or "bdh 1296" or bdh1296 or borea or endace* or linmegestrol* or maygace* or megace* or megaplex* or megase* or megastrol* or megefren* or megejohn* or megestat* or megestil* or megestranol* or megestrinol* or megostat* or mergestrol* or mestrel* or niagestin* or numegestrol* or ovaban* or ovarid* or pallace* or "sc 10363" or sc10363) 502
#22 MeSH descriptor: [Mitoxantrone] this term only 375
#23 (mitoxantron* or "cl 232" or "cl 232315" or cl232 or cl232315 or "cl 232325" or cl232325 or dhad* or dhaq* or domitrone* or elsep* or formyxan* or misostol* or mitoxanthron* or mitoxgen* or mitozantron* or mitroxantron* or mitroxon* or neotalem* or norexan* or novanthron* or novantron* or "now 85 34" or "now85 34" or "now 8534" or now8534 or "nsc 279836" or nsc279836 or "nsc 301739" or nsc301739 or "nsc 301739d" or nsc301739d or "nsc 299195" or nsc299195 or nsc287836 or "nsc 287836" or oncotron* or onkotron* or pralifan* or ralenova*) 1008
#24 MeSH descriptor: [Prednisone] this term only 2837
#25 (prednison* or ancortone* or apoprednisone* or biocortone* or colisone* or cortan* or cortidelt* or cortiprex* or cutason* or dacorten* or dacortin* or de next cortisyl* or decortancyl* or decortin* or decortisyl* or dehydrocortisone* or dekortin* or delitisone* or dellacort* or delta next cortelan* or delta next cortisone* or delta next dome* or delta next e* or delta next prenovis* or delta next sone* or deltadome* or deltacorten* or deltacortisone* or deltacortone* or deltasone* or deltison* or deltra* or di next adreson* or diadreson* or drazone* or encorton* or enkorton* or enkortolon*

or fernisone* or hostacortin* or insone* or kortancyl* or liquid next pred* or lodotra* or me-korti* or mekorti* or meprison* or metacortandracin* or meticorten* or meticortine* or nisona* or nsc next 10023* or nsc10023* or orasone* or orisane* or panafcort* or panasol* or paracort* or pehacort* or precort* or predni next tablinen* or prednicen* or prednicorm* or prednicot* or prednidib* or predniment* or prednitone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servisone* or sone or steerometz* or sterapred* or ultracorten* or urtilone* or winpred*) 8920
#26 {or #5-#25} 13393
#27 #4 and #26 in Technology Assessments 36

A.8: Source: Cochrane Central Register of Controlled Trials (Central) Issue 9 of 12, Sept 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 22/10/14
Retrieved records: 873
Search strategy:

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3404
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 32
#3 (prostate or prostatic) 10487
#4 {or #1-#3} 10487
#5 (enzalutamide or xtandi*) 13
#6 ("MDV 3100" or mdv3100) 4
#7 (abiraterone or zytiga*) 34
#8 sipuleucel* 26
#9 (apc8015 or provenge*) 17
#10 (docetaxel or taxotere*) 2210
#11 (radium-223 or ra223 or ra-223 or xofigo* or alpharadin*) 16
#12 MeSH descriptor: [Flutamide] this term only 281
#13 (flutamid* or apimid* or apoflutamide* or chimax* or cytamid* or drogenil* or etaconil* or euflex* or eulexin* or flucinom* or fludinom* or flugerel* or fluken* or flulem* or flumid* or fluta next cell* or fluta next gry* or fluta next la next pharma* or flutacell* or flutagry* or flutamex* or flutamin* or flutan* or flutaplex* or flutax* or flutexin* or flutol* or fluxus* or fugerel* or grisetin* or niftolid* or niphtholid* or novoflutamide* or odyne* or oncosal* or pmsflutamide* or prostacur* or prostamid* or prostica* or prostogenat* or restotard* or "sch 13521" or sch13521 or sebatrol* or tafenil* or testac* or testotard*) 457
#14 (bicalutamid* or casodex* or cosudex* or calutide* or "ici 176334" or ici176334 or kalumid* or lutamidal* or raffolutil*) 203
#15 (nilutamid* or anadron* or anandron* or canandron* or nilandron* or nitulamide* or "rn 23908" or rn23908 or "ru 23908" or ru23908) 58
#16 MeSH descriptor: [Cyproterone] this term only and with qualifier(s): [Analogs & derivatives - AA] 66

#17 MeSH descriptor: [Cyproterone Acetate] this term only 255
#18 (cyproteron* or androcur* or cyprostat* or cyproterane next acetate* or "nsc 81340" or nsc81340 or "nsc 81430" or nsc81430 or "sh 714" or sh714 or sinovir* or virilit*) 499
#19 MeSH descriptor: [Megestrol] this term only and with qualifier(s): [Analogs & derivatives - AA] 68
#20 MeSH descriptor: [Megestrol Acetate] this term only 159
#21 (megestrol* or apomegestrol* or "bdh 1296" or bdh1296 or borea or endace* or linmegestrol* or maygace* or megace* or megaplex* or megase* or megastrol* or megefren* or megejohn* or megestat* or megestil* or megestranol* or megestrinol* or megostat* or mergestrol* or mestrel* or niagestin* or numegestrol* or ovaban* or ovarid* or pallace* or "sc 10363" or sc10363) 502
#22 MeSH descriptor: [Mitoxantrone] this term only 375
#23 (mitoxantron* or "cl 232" or "cl 232315" or cl232 or cl232315 or "cl 232325" or cl232325 or dhad* or dhaq* or domitrone* or elsep* or formyxan* or misostol* or mitoxanthron* or mitoxgen* or mitozantron* or mitroxantron* or mitroxon* or neotalem* or norexan* or novanthron* or novantron* or "now 85 34" or "now85 34" or "now 8534" or now8534 or "nsc 279836" or nsc279836 or "nsc 301739" or nsc301739 or "nsc 301739d" or nsc301739d or "nsc 299195" or nsc299195 or nsc287836 or "nsc 287836" or oncotron* or onkotron* or pralifan* or ralenova*) 1008
#24 MeSH descriptor: [Prednisone] this term only 2837
#25 (prednison* or ancortone* or apoprednisone* or biocortone* or colisone* or cortan* or cortidelt* or cortiprex* or cutason* or dacorten* or dacortin* or de next cortisyl* or decortancyl* or decortin* or decortisyl* or dehydrocortisone* or dekortin* or delitisone* or dellacort* or delta next cortelan* or delta next cortisone* or delta next dome* or delta next e* or delta next prenovis* or delta next sone* or deltadome* or deltacorten* or deltacortisone* or deltacortone* or deltasone* or deltison* or deltra* or di next adreson* or diadreson* or drazone* or encorton* or enkorton* or enkortolon* or fernisone* or hostacortin* or insone* or kortancyl* or liquid next pred* or lodotra* or me-korti* or mekorti* or meprison* or metacortandracin* or meticorten* or meticortine* or nisona* or nsc next 10023* or nsc10023* or orasone* or orisane* or panafcort* or panasol* or paracort* or pehacort* or precort* or predni next tablinen* or prednicen* or prednicorm* or prednicot* or prednidib* or predniment* or prednitone* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servisone* or sone or steerometz* or sterapred* or ultracorten* or urtilone* or winpred*) 8920
#26 {or #5-#25} 13393
#27 #4 and #26 in Trials 873

A.9: Source: ClinicalTrials.gov

Interface / URL: http://clinicaltrials.gov/ct2/home
Search date: 22/10/14
Retrieved records: 610

Search strategy:

Following searches carried out. Terms entered in 'Search Terms' box in advnaced search interface (http://clinicaltrials.gov/ct2/search/advanced)

1. enzalutamide OR xtandi OR "mdv 3100" OR mdv3100 OR "915087-33-1" OR 93T0T9GKNU = 79

2. (prostate OR prostatic) AND (abiraterone OR zytiga OR "154229-19-3" OR G819A456D0) = 109

3. (prostate OR prostatic) AND (docetaxel OR taxotere OR "114977-28-5" OR 699121PHCA OR "148408-66-6" OR 15H5577CQD) = 358

4. "radium-223" OR ra223 OR "ra-223" OR xofigo OR alpharadin OR "444811-40-9" OR RJ00KV3VTG = 33

5. sipuleucel OR "sipuleucel-T" or sipuleucelT OR apc8015 OR provenge OR "917381-47-6" OR 8Q622VDR18 = 31

A.10: Source: International Clinical Trials Registry Platform (ICTRP)

Interface / URL: http://apps.who.int/trialsearch/
Search date: 23/10/14
Retrieved records: 724
Search strategy:

Basic search interface at the above url used. Following searches run:

1. enzalutamide OR xtandi* OR mdv 3100 OR mdv3100 OR 915087-33-1 OR 93T0T9GKNU OR abiraterone OR zytiga* OR 154229-19-3 OR G819A456D0 OR radium-223 OR ra223 OR ra-223 OR xofigo* OR alpharadin* OR 444811-40-9 OR RJ00KV3VTG OR sipuleucel* OR apc8015 OR provenge* OR 917381-47-6 OR 8Q622VDR18 = 247 (459 records for 247 trials)

2. docetaxel AND prostate OR taxotere* AND prostate = 413 (686 records for 413 trials)

3. docetaxel AND prostatic OR taxotere* AND prostatic = 47 (83 records for 47 trials)

4.114977-28-5 AND prostate OR 699121PHCA AND prostate OR 148408-66-6 AND prostate OR 15H5577CQD AND prostate = 17 (52 records for 17 trials)

5. 114977-28-5 AND prostatic OR 699121PHCA AND prostatic OR 148408-66-6 AND prostatic OR 15H5577CQD AND prostatic = 0 results

A.11: Source: metaRegister of Controlled Trials (mRCT)

Interface / URL: http://www.controlled-trials.com/mrct/
Search date: 23/10/14
Retrieved records: 10
Search strategy:

All registers selected for search apart from the NIH ClinicalTrials.gov Register (searched via ct.gov and ICTRP - see above). Following searches carried out – terms entered in search box at: http://www.controlled-trials.com/mrct/searchform.

1. enzalutamide OR xtandi OR mdv3100 OR abiraterone OR zytiga OR ra223 OR xofigo OR alpharadin OR sipuleucel OR sipuleucel-T or sipuleucelT OR apc8015 OR provenge = 1

2. mdv 3100 = 0 results

3. mdv-3100 = 0 results

4. radium-223 = 0 results

5. radium 223 = 0 results

6. ra-223 = 0 results

7. ra 223 = 0 results

8. docetaxel AND prostate = 7

9. taxotere AND prostate = 2

10. docetaxel AND prostatic = 0 results

11. taxotere AND prostatic = 0 results

A.12: Source: NHS Economic Evaluation Database (NHS EED) - Issue 3 of 4, July 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 23/10/14
Retrieved records: 3
Search strategy:

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 3404
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 32

#3 (prostate or prostatic) 10487
#4 {or #1-#3} 10487
#5 (enzalutamide or xtandi*) 13
#6 ("MDV 3100" or mdv3100) 4
#7 (abiraterone or zytiga*) 34
#8 sipuleucel* 26
#9 (apc8015 or provenge*) 17
#10 (radium-223 or ra223 or ra-223 or xofigo* or alpharadin*) 16
#11 {or #5-#10} 92
#12 (docetaxel or taxotere*) 2210
#13 #4 and #12 236
#14 #11 or #13 in Economic Evaluations 3

A.13: Source: Health Economic Evaluations Database (HEED)

Interface / URL: EBSCOHost
Search date: 23/10/14
Retrieved records: 9
Search strategy:

TX (enzalutamide or xtandi* or "MDV 3100" or mdv3100 or abiraterone or zytiga* or sipuleucel* or apc8015 or provenge* or "radium-223" or ra223 or "ra-223" or xofigo* or alpharadin*) or TX ((prostate OR prostatic) AND (docetaxel or taxotere*))

A.14: Source: Econlit 1886 to September 2014

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 3
Search strategy:

1 (enzalutamide or xtandi$ or mdv 3100 or mdv3100 or abiraterone or zytiga$ or docetaxel or taxotere$ or radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$ or sipuleucel$ or apc8015 or provenge$).af. 3

A.15: Source: Cost-effectiveness Analysis (CEA) Registry

Interface / URL: https://research.tufts-nemc.org/cear4
Search date: 23/10/14
Retrieved records: 7
Search strategy:

Basic search interface used at:

https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx. Following searches run:

enzalutamide = 0
xtandi = 0
mdv 3100 = 0
mdv-3100 = 0
mdv3100 = 0
abiraterone = 1
zytiga = 0
docetaxel = 32
taxotere = 4
radium 223 = 0
radium-223 = 0
ra223 = 0
ra 233 = 0
ra-223 = 0
xofigo = 0
alpharadin = 0
sipuleucel = 0
sipuleucel-T = 0
sipuleucelT = 0
apc8015 = 0
provenge = 0

37 records identified. 7 retrieved for assessment

A.16: Source: National Institute for Health and Clinical Excellence (NICE)

Interface / URL: http://www.nice.org.uk/

Search date: 24/10/14
Retrieved records: 7
Search strategy:

Searched the following terms using the search box on the NICE home page at the above url.

enzalutamide
xtandi
mdv 3100
mdv-3100

mdv3100
abiraterone
zytiga
docetaxel [results limited by ‘Conditions and Diseases’ to Cancer
taxotere
radium-223
radium 223
ra223
ra 223
ra-223
xofigo
alpharadin
sipuleucel-t
sipuleucel t
sipuleucelt
sipuleucel
apc8015
provenge

A.17: Source: Agency for Healthcare Research and Quality (AHRQ)

Interface / URL: http://www.ahrq.gov/index.html

Search date: 24/02/14
Retrieved records: 1
Search strategy:

Following searches conducted and results assessed. Relevant results downloaded.

1. Using the advanced search option, searched the following terms (in the ‘with at least one of the words’ search box):

enzalutamide xtandi abiraterone zytiga xofigo alpharadin sipuleucelt sipuleucel apc8015 provenge mdv3100 ra223

2. Using the advanced search option searched the following terms (in the ‘with the exact phrase’ box):

mdv 3100
mdv-3100
radium-223
radium 223
ra223
ra 223

ra-223
sipuleucel-t
sipuleucel t

3. Using the advanced search option searched the following terms (in the 'with all of the words' box):

docetaxel prostate
docetaxel prostatic
taxotere prostate
taxotere prostatic

A.18: Source: Canadian Agency for Drugs and Technologies in Health (CADTH)

Interface / URL: http://www.cadth.ca/en
Search date: 23/10/14
Retrieved records: 1
Search strategy:

Searched via the 'Search All Canadian HTA websites' page: http://www.cadth.ca/en/search/federated

Following terms searched:

enzalutamide
xtandi
mdv 3100
mdv-3100
mdv3100
abiraterone
zytiga
docetaxel
taxotere
radium-223
radium 223
ra223
ra 223
ra-223
xofigo
alpharadin
sipuleucel-t
sipuleucel t
sipuleucelt
sipuleucel

apc8015
provenge

A.19: Source: Scottish Intercollegiate Guidelines Network (SIGN)

Interface / URL: http://www.sign.ac.uk/index.html
Search date: 23/10/14
Retrieved records: 0
Search strategy:

1. Scanned list of guidelines for relevant.

2. Using site search engine (at: http://www.sign.ac.uk/search.html) searched on following terms:

enzalutamide
xtandi
mdv 3100
mdv-3100
mdv3100
abiraterone
zytiga
docetaxel
taxotere
radium-223
radium 223
ra223
ra 223
ra-223
xofigo
alpharadin
sipuleucel-t
sipuleucel t
sipuleucelt
sipuleucel
apc8015
provenge

A.20: Source: U.S. Food and Drug Administration (FDA)

Interface / URL: http://www.fda.gov/

Search date: 24/10/14
Retrieved records: 5
Search strategy:

Searched drugsa@fda (via: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) using the following terms:

enzalutamide
xtandi
mdv 3100
mdv-3100
mdv3100
abiraterone
zytiga
docetaxel
taxotere
radium-223
radium-223
ra223
ra 223
ra-223
xofigo
alpharadin

Using main search box at http://www.fda.gov/BiologicsBloodVaccines/default.htm, searched on the following terms:

sipuleucel-t
sipuleucel t
sipuleucelt
sipuleucel
apc8015
provenge

A.21: Source: European Medicines Agency (EMA)

Interface / URL: http://www.ema.europa.eu/ema/

Search date: 24/10/14
Retrieved records: 5
Search strategy:

Via the European Public Assessments Report page (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124) used A – Z browse function to naviage to page for each of following medicines: xtandi, zytiga, taxotere, xofigo, provenge.

Links to relevant pages downloaded.

A.22: Source: American Society of Clinical Oncology (ASCO) Annual Meeting and GU Cancers Symposium

Interface / URL: http://www.asco.org/meetings

Search date: 24/10/14

Retrieved records: 67

Search strategy:

ASCO Annual Meeting 2014 (May 30 – June 3, Chicago)

All abstracts searchable at:

http://meetinglibrary.asco.org/subcategories/2014%20ASCO%20Annual%20Meeting

Prostate cancer abstracts:

http://meetinglibrary.asco.org/abstractbysubcategory/2014%20ASCO%20Annual%20Meeting/559

5 records retrieved

ASCO Annual Meeting 2013 (May 31 – June 4, Chicago)

Abstracts searchable at http://meetinglibrary.asco.org/VMTracks/2013%20ASCO%20Annual%20Meeting

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

22 records retrieved

ASCO Annual Meeting 2012 (June 1 – June 5, Chicago)

Abstracts searchable at

http://meetinglibrary.asco.org/VMTracks/2012%20ASCO%20Annual%20Meeting

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

9 records retrieved

ASCO Annual Meeting 2011 (June 3 – June 6, Chicago)

Abstracts searchable at

http://meetinglibrary.asco.org/subcategories/2011%20ASCO%20Annual%20Meeting

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

7 records retrieved

ASCO 2014 Genitourinary Cancers Symposium January 30 – February 1 2014 San Francisco

Abstracts searchable at

http://meetinglibrary.asco.org/subcategories/2014%20Genitourinary%20Cancers%20Symposium

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

7 records retrieved

ASCO 2013 Genitourinary Cancers Symposium February 14 – February 16 2013 Orlando Florida

Abstracts searchable at

http://meetinglibrary.asco.org/VMTracks/2013%20Genitourinary%20Cancers%20Symposium?media=vm

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

12 records retrieved

ASCO 2012 Genitourinary Cancers Symposium February 2 – February 4 2014 San Francisco

Abstracts searchable at

http://meetinglibrary.asco.org/subcategories/2012%20Genitourinary%20Cancers%20Symposium

Following terms searched for in the body text:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

5 records retrieved

A.23: Source: American Urological Association Annual Meeting

Interface / URL: see below

Search date: 14/02/14

Retrieved records: 9

Search strategy:

AUA Annual Meeting 2014 May 16 – May 21 Orlando

Searching in http://www.aua2014.org/program/ by keyword for the following search terms. Log in required to access full text.

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

Records retrieved 0

AUA Annual Meeting 2013 May 4 – May 8 San Diego

Abstracts searchable at http://www.aua2013.org/abstracts/index2.cfm

Following terms searched for as keywords:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

5 records retrieved

AUA Annual Meeting 2012 May 19 – May 23 San Diego

Abstracts searchable at http://www.aua2012.org/abstracts/abstracts.cfm but system error when searches took place 14 February 2014 “Our system is undergoing maintenance. 2012 Abstract search is temporarily unavailable. Sorry for the inconvenience.”

Following terms searched for as keywords via the “search within this issue function” on the Journal of Urology webpages. Abstracts included as a supplement to Vol 187 No 4 :

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

3 records retrieved

AUA Annual Meeting 2011 May 14 – May 19 Washington DC

Following terms searched for as keywords via the “search within this issue function” on the Journal of Urology webpages. Abstracts included as a supplement to Vol 186 No 6 :

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

1 record retrieved

A.24: Source: European Association of Urology Annual Congress

Interface / URL: http://www.uroweb.org/events/

Search date: 24/10/14

Retrieved records: 9

Search strategy:

EAU Annual Congress 2014 11-15 April Stockholm

Abstracts searchable via: http://eaustockholm2014.uroweb.org/

Can only search title field. Following terms used:

Enzalutamide

Xtandi

Mdv 3100

Mdv3100

Abiraterone

Zytiga

Docetaxel

Taxotere

Radium-223

Ra223

Ra 223

Xofigo

Alpharadin

Sipuleucel-t.

Apc8015

Provenge

EAU Annual Congress 2013 15-19 March Milan

Abstracts searchable via: http://www.uroweb.org/events/abstracts-online/.

Can only search title field. Following terms used:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

Full abstract embargoed until April 2014 – title and authors only.

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

5 records retrieved

EAU Annual Congress 2012 24-28 February Paris

Abstracts searchable via http://www.uroweb.org/events/abstracts-online/.

Can only search title field. Following terms used:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

Full abstract embargoed until April 2014 – title and authors only.

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

1 record retrieved

EAU Annual Congress 2011 18-22 March Vienna

Abstracts searchable via http://www.uroweb.org/events/abstracts-online/.

Can only search title field. Following terms used:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

Full abstract embargoed until April 2014 – title and authors only.

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

2 records retrieved

A.25: Source: European Society for Medical Oncology Congress

Interface / URL: http://www.esmo.org/Conferences/Past-Conferences

Search date: 24/10/14
Retrieved records: 6
Search strategy:

ESMO Congress 2014 26 Sept – 30 Sept Madrid

http://www.esmo.org/Conferences/ESMO-2014-Congress

Abstracts available alphabetically via:

https://www.webges.com/cslide/library/esmo/browse/search/e4d

Search abstract text for the following:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

2 records retrieved

ESMO 2013 – no congress held [ECCO instead]

ESMO Congress 2012 28 Sept – 2 Oct Vienna Austria

Abstracts searchable via http://abstracts.webges.com/esmo2012/myitinerary

Search abstract text for the following:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

4 records retrieved

ESMO 2011 – congress held jointly with ECCO – see below

A.26: Source: European CanCer Organisation Congress (ECCO)

Interface / URL: http://www.ecco-org.eu/Events/Past-conferences.aspx

Search date: 24/10/14
Retrieved records: 17
Search strategy:

Next upcoming event:

European Cancer Congress 2015 (ECC2015)
http://www.ecco-org.eu/Events/ECC2015.aspx

Two past events identified relevant to the search since Feb 2014:

EONS9 (European Oncology Nursing Society)
EACR23 (European Association for Cancer Research) biennial

The European Cancer Congress 2014 was organised by ESMO (see above).

The European Cancer Congress 2013, Amsterdam 27 Sep - 1 Oct 2013

Abstracts searchable via http://eccamsterdam2013.ecco-org.eu/Scientific-Programme/Abstract-search.aspx

Searched abstract body for the following:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel AND prostate
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

16 records retrieved

No conference 2012

16th ECCO, 36th ESMO, 30th ESTRO Congresses, Stockholm 23-27 Sep 2011

Abstracts available via European Journal of Cancer Vol 47 Suppl 1 2011 – searched the issue via the Science Direct

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

1 record retrieved

ESMO 2011 – congress held jointly with ECCO – see below

A.26: Source: European CanCer Organisation Congress (ECCO)

Interface / URL: http://www.ecco-org.eu/Events/Past-conferences.aspx

Search date: 24/10/14
Retrieved records: 17
Search strategy:

Next upcoming event:
European Cancer Congress 2015 (ECC2015)
http://www.ecco-org.eu/Events/ECC2015.aspx

Two past events identified relevant to the search since Feb 2014:

EONS9 (European Oncology Nursing Society)

EACR23 (European Association for Cancer Research) biennial

The European Cancer Congress 2014 was organised by ESMO (see above).

The European Cancer Congress 2013, Amsterdam 27 Sep - 1 Oct 2013

Abstracts searchable via http://eccamsterdam2013.ecco-org.eu/Scientific-Programme/Abstract-search.aspx

Searched abstract body for the following:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga

Docetaxel AND prostate
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

16 records retrieved

No conference 2012

16th ECCO, 36th ESMO, 30th ESTRO Congresses, Stockholm 23-27 Sep 2011

Abstracts available via European Journal of Cancer Vol 47 Suppl 1 2011 – searched the issue via the Science Direct

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin

Sipuleucel-t.
Apc8015
Provenge

RCTs or economic evaluations of any eligible interventions, single arm trials of Enzalutimde, or studies reporting resource use in mCRPC selected.

1 record retrieved

A.27: Source: International Society for Quality of Life Research (ISOQOL) Annual Conference

Interface / URL: http://www.isoqol.org/annual-conference

Search date: 24/10/14
Retrieved records: 0
Search strategy:

2015 Annual Conference

http://www.isoqol.org/annual-conference/2015-annual-conference

ISOQOL 2014 15-18 October 2014

http://www.isoqol.org/2014conference

Programme available in PDF at:

http://www.isoqol.org/UserFiles/ISOQOL21stAnnualConferenceProgram.pdf

Abstracts not available yet.

Used find function for searching in the entire website by the search terms bellow. Only one results found, not relevant.

ISOQOL 20th Annual Conference Miami, Florida, United States, October 9-12, 2013

Programme searchable at http://www.isoqol.org/UserFiles/file/2013_Program.pdf

Used find function for following terms:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

0 records retrieved

ISOQOL 19th Annual Conference Budapest, Hungary, October 24-27, 2012

Programme searchable at http://www.isoqol.org/UserFiles/file/ac12-final-v9.pdf

Used find function for following terms:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo

Alpharadin
Sipuleucel-t.
Apc8015
Provenge

0 records retrieved

ISOQOL 18th Annual Conference Denver, Colorado, United States, October 26-29, 2011

Programme searchable at http://www.isoqol.org/UserFiles/file/2011_conference_program.pdf

Used find function for following terms:

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

0 records retrieved

A.28: Source: International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Interface / URL: See below

Search date: 18/02/14
Retrieved records: 16

Search strategy:

Past meetings since last search in Feb 2014:

ISPOR Annual International Meeting

19th Annual Meeting

Abstracts available at:

http://www.ispor.org/publications/value/VIH_17-3_final.pdf

Search text using the search functionality

12 records identified- none relevant

ISPOR 16TH Annual European Congress 2-6 November 2013 Dublin

Abstracts available in Value in Health Vol 16 No 7 2013 http://www.valueinhealthjournal.com/

Searched within journal issues – keywords – all fields using the following terms

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

8 records retrieved

ISPOR 15TH Annual European Congress 3-7 November 2013 Berlin

Abstracts available in Value in Health Vol 16 No 7 2013 http://www.valueinhealthjournal.com/

Searched within journal issues – keywords – all fields using the following terms

Enzalutamide
Xtandi
Mdv 3100
Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

7 records retrieved

ISPOR 14TH Annual European Congress 5-8 November 2013 Madrid

Abstracts available in Value in Health Vol 14 No 7 2011 http://www.valueinhealthjournal.com/

Searched within journal issues – keywords – all fields using the following terms

Enzalutamide
Xtandi
Mdv 3100

Mdv3100
Abiraterone
Zytiga
Docetaxel
Taxotere
Radium-223
Ra223
Ra 223
Xofigo
Alpharadin
Sipuleucel-t.
Apc8015
Provenge

1 record retrieved

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were conducted.

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria of the systematic literature review are presented in section 6.2.1; Table B2.

10.2.7 The data abstraction strategy.

A data extraction form was designed to collect the methodology, endpoints and outcomes of the selected studies. Once all relevant studies had been identified, the relevant data were extracted and included in this data extraction form.

Studies selected for abstraction were data extracted by one reviewer, with quality checking undertaken on a sample of records by a second reviewer. Any discrepancies were resolved by a third reviewer.

The risk of bias in the identified RCTs was assessed using the quality elements suggested in the NICE STA guidance. The following quality criteria were assessed:

- What was the method of randomization?
- Was the treatment allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors (e.g. severity of disease)?

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table D2 Quality assessment of PREVAIL

Study ID or acronym:	**PREVAIL**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	The study was centrally randomised by IVRS using a permuted block method. Randomisation was stratified by study site. Patients were randomised in a 1:1 ratio to receive oral enzalutamide or matched placebo capsules	Yes
Was the concealment of treatment allocation adequate?	All patients, investigators, site personnel, and sponsor personnel involved in the conduct of the study were blinded to treatment assignment.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	All patients, investigators, and the sponsor's staff involved in the conduct of the study were blinded to treatment assignment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		No

Is there any evidence to suggest that the authors measured more outcomes than they reported?		No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Missing data were imputed for primary outcomes	Yes Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched for the indirect treatment comparison are the same as those in section 10.2.1.

10.4.2 The date on which the search was conducted.

See section 10.2.2.

10.4.3 The date span of the search.

See section 10.2.3.

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used to identify relevant studies for the indirect treatment comparison are the same as those in section 10.2.4.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.4.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria of the systematic literature review are presented in section 6.2.1; Table B2.

10.4.7 The data abstraction strategy.

The data abstraction strategy for the indirect treatment comparison was the same strategy described in section 10.2.7.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table D3 Quality assessment of COU-AA-302

Study ID or acronym:	**COU-AA-302**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**

Study ID or acronym:	COU-AA-302	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	The randomisation schedule was generated by an independent statistician. Patients were assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Patient eligibility was verified by the investigators, who then entered the stratification factor (i.e. baseline ECOG PS grade [0 versus 1]) into the IWRS/IVRS system.	Yes*
Was the concealment of treatment allocation adequate?	All patients, family members, study personnel and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the exception of the circumstances described in the text below regarding blinding of treatment allocation. The matched placebo tablets given to patients in the placebo arm were also visually indistinguishable from the abiraterone acetate tablets.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	With a few exceptions, demographics and disease characteristics were balanced between the two treatment groups. The few differences in demographics and disease characteristics were not considered clinically relevant.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	All patients, family members, study personnel, and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the following exceptions: The Independent Biostatistician and Independent Statistical Programmer responsible for preparing interim tables, listings, and graphs for IDMC review were not blinded. It is not clear whether the IDMC was blinded or not.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No imbalances in dropouts between groups were observed	No*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The clinical study report and associated journal and conference publications for the COU-AA-302 study were available and were reviewed. There was no indication that the clinical study report did not include all the measured outcomes	No*
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population included all patients randomised into the study; patients were to be classified according to assigned treatment group, regardless of the actual treatment received. The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.	Yes, no reporting of missing data methods
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

*The published articles do not provide these data but they are available from the NICE manufacturer submission of abiraterone in the chemo-naïve setting[35].

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched for the indirect treatment comparison are the same as those in section 10.2.1.

10.6.2 The date on which the search was conducted.

See section 10.2.2.

10.6.3 The date span of the search.

See section 10.2.3.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used to identify relevant non randomised clinical studies are the same as those in section 10.2.4.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.6.6 The inclusion and exclusion criteria.

The data abstraction strategy for non-randomised clinical trials was the same strategy described in section 10.2.7.

10.6.7 The data abstraction strategy.

The data abstraction strategy for non-randomised clinical trials was the same strategy described in section 10.2.7.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Scher et al was the only non-RCT identified. This study is a dose-finding study which included a mixed population of chemo-naïve (N=12) and post-chemo patients (N=12). Patients received one of the following daily doses of enzalutamide: 30, 60, 150, 240, 360, 480 and 600 mg/day. The study does not provide separate data for chemo-naïve and post-chemo patients and thus, it is not included here.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- The Cochrane Library.

No separate searches were conducted to identify safety studies. However, AEs were included as an outcome of interest in the overarching systematic review. The databases used to identify studies providing safety data are the same as those listed in Table D1.

10.8.2 The date on which the search was conducted.

See section 10.2.2.

10.8.3 The date span of the search.

See section 10.2.3.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used to identify relevant safety studies are the same as those in section 10.2.4.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.8.6 The inclusion and exclusion criteria.

The data abstraction strategy for safety studies was the same strategy described in section 10.2.7.

10.8.7 The data abstraction strategy.

The data abstraction strategy for non-randomised clinical trials was the same strategy described in section 10.2.7.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

No additional studies to those already assessed in Table D2 (PREVAIL) and Table D3 (COU-AA-302) were identified.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

The databases used to identify economic studies are the same as those listed in Table D1 for clinical studies.

10.10.2 The date on which the search was conducted.

See section 10.2.2.

10.10.3 The date span of the search.

See section 10.2.3.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

No separate searches were conducted to identify economic studies. The search strategies are the same as those described in section 10.2.4.

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

No economic study assessing enzalutamide in the chemo-naïve setting was identified. However, an assessment of abiraterone in this setting was reviewed for this submission.

	Study name: Manufacturer NICE submission for abiraterone in the chemo-naïve setting	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	The outcomes were treated as commercial in confidence

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The databases searched are given in Table D4.

Table D4 Databases searched and provider used for identification of health effects

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
EMBASE	OvidSP
EconLit	OvidSP
NHS Economic Evaluation Database (NHS EED)	http://www.crd.york.ac.uk/crdweb/
Health Economic Evaluation Database (HEED)	EBSCOHost
Cost-Effectiveness Analysis (CEA)	https://research.tufts-

Registry	nemc.org/cear4/Home.aspx
Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)	http://www.proqolid.org/
Health Technology Assessment Database (HTA Database)	http://www.crd.york.ac.uk/crdweb/
Scottish Medicines Consortium (SMC)	http://www.scottishmedicines.org.uk/Home
Pharmaceutical Benefits Advisory Committee (PBAC)	http://www.pbs.gov.au/pbs/home
NICE	http://www.nice.org.uk/
Pan-Canadian Oncology Drug Review (pCODR)	http://www.pcodr.ca/wcpc/portal/
Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)	http://www.tlv.se/

10.12.2 The date on which the search was conducted.

All searches were conducted on 23 October 2014.

10.12.3 The date span of the search.

No date limits were applied.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies used are given below.

Table D5 Search strategy in MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) 1946 to Present

1 Prostatic Neoplasms/ (98481)
2 Prostatic Intraepithelial Neoplasia/ (1293)
3 (prostat$ adj3 (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).ti,ab,kf. (104272)
4 or/1-3 (121891)
5 exp Neoplasm Metastasis/ (162244)
6 exp Bone Neoplasms/ (104098)
7 Drug Resistance, Neoplasm/ (30442)
8 (metastat$ or meta-stat$ or metastas$ or meta-stas$ or disseminat$ or spread$ or migrat$).ti,ab,kf. (736636)

9 (castrat$ and (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (4762)
10 (hormone$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (5529)
11 (androgen$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (3922)
12 (M1 or M1a or M1b or M1c).ti,ab,kf. (23693)
13 (D1 or D2).ti,ab,kf. (57638)
14 ("stage 4" or "stage4" or stage IV or stageIV).ti,ab,kf. (19456)
15 advanced.ti,ab,kf. (273606)
16 or/5-15 (1207912)
17 4 and 16 (38741)
18 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).ti,ab,kf. (2391)
19 Prostatic Neoplasms, Castration-Resistant/ (373)
20 17 or 18 or 19 (38949)
21 Quality-Adjusted Life Years/ (7551)
22 (quality adjusted or adjusted life year$).ti,ab,kf. (8894)
23 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (5821)
24 disability adjusted life.ti,ab,kf. (1452)
25 daly$1.ti,ab,kf. (1379)
26 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf. (401)
27 (multiattribute$ or multi attribute$).ti,ab,kf. (536)
28 (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or scale$1 or instrument$1 or score$1)).ti,ab,kf. (7953)
29 (disutility or disutilities).ti,ab,kf. (255)
30 health$1 year$1 equivalent$1.ti,ab,kf. (40)
31 (hye or hyes).ti,ab,kf. (57)
32 (hui or hui1 or hui2 or hui3).ti,ab,kf. (993)
33 (illness state$1 or health state$1).ti,ab,kf. (4151)
34 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf. (4633)
35 (short form$ or shortform$).ti,ab,kf. (19611)
36 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (15037)
37 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf. (2363)
38 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (2554)
39 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf. (19)
40 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf. (314)
41 standard gamble$.ti,ab,kf. (710)
42 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1279)
43 (factc or fact-c or factp or fact-p).ti,ab,kf. (174)
44 (PC-QoL or PCQOL or PORPUS or PROSQOLI or PROS-QOLI).ti,ab,kf. (37)
45 (QOLM-P14 or QOLMP14).ti,ab,kf. (1)
46 or/21-45 (55644)
47 "cost of illness"/ (18844)
48 exp health care costs/ (48865)

49 "Costs and Cost Analysis"/ (42927)
50 cost-benefit analysis/ (62786)
51 (cost or costs).ti,ab,kf. (340479)
52 (costing adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf. (100)
53 (burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf. (18411)
54 (resource$1 adj4 (use$1 or usage or utilit$)).ti,ab,kf. (19098)
55 (economic evaluation$ or pharmacoeconomic$).ti,ab,kf. (10380)
56 (hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized).ti,ab,kf. (159076)
57 (admission$1 or readmission$1 or admitted or readmitted or visit or visits).ti,ab,kf. (362379)
58 (bed adj2 days).ti,ab,kf. (1810)
59 hospital stay$1.ti,ab,kf. (51559)
60 ((days or time or length or duration$1) adj3 hospital$).ti,ab,kf. (54832)
61 ((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kf. (57498)
62 ((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kf. (14436)
63 or/47-62 (931325)
64 46 or 63 (968972)
65 20 and 64 (1473)
66 exp animals/ not humans/ (4079856)
67 65 not 66 (1469)
68 (news or comment or editorial or letter or case reports).pt. (3104316)
69 case report.ti. (165536)
70 67 not (68 or 69) (1275)
71 remove duplicates from 70 (1204)

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 1204

Table D6 Search strategy in Embase 1974 to 2014 October 22

1 exp *prostate tumor/ (108202)
2 (prostat$ adj3 (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).ti,ab,kw. (134058)
3 1 or 2 (146427)
4 *metastasis/ (54275)
5 *drug resistance/ (27795)
6 (metastat$ or meta-stat$ or metastas$ or meta-stas$ or disseminat$ or spread$ or migrat$).ti,ab,kw. (892767)

7 (castrat$ and (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (7086)
8 *hormone resistance/ (930)
9 (hormone$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (6742)
10 (androgen$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (4567)
11 (M1 or M1a or M1b or M1c).ti,ab,kw. (30583)
12 (D1 or D2).ti,ab,kw. (73341)
13 ("stage 4" or "stage4" or stage IV or stageIV).ti,ab,kw. (28707)
14 *advanced cancer/ (15079)
15 advanced.ti,ab,kw. (361423)
16 or/4-15 (1345291)
17 3 and 16 (46249)
18 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).ti,ab,kw. (4342)
19 *castration resistant prostate cancer/ (2441)
20 exp *prostate tumor/dr (865)
21 17 or 18 or 19 or 20 (46774)
22 *quality adjusted life year/ (802)
23 (quality adjusted or adjusted life year$).ti,ab,kw. (11422)
24 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. (9364)
25 disability adjusted life.ti,ab,kw. (1630)
26 daly$1.ti,ab,kw. (1734)
27 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kw. (571)
28 (multiattribute$ or multi attribute$).ti,ab,kw. (665)
29 (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or scale$1 or instrument$1 or score$1)).ti,ab,kw. (10726)
30 (disutility or disutilities).ti,ab,kw. (391)
31 health$1 year$1 equivalent$1.ti,ab,kw. (42)
32 (hye or hyes).ti,ab,kw. (99)
33 (hui or hui1 or hui2 or hui3).ti,ab,kw. (1356)
34 (illness state$1 or health state$1).ti,ab,kw. (5976)
35 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw. (7533)
36 *short form 12/ or *short form 20/ or *short form 36/ or *short form 8/ or *short form 6D/ (547)
37 (short form$ or shortform$).ti,ab,kw. (23524)
38 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. (21836)
39 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kw. (2938)
40 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw. (3912)
41 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kw. (31)
42 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kw. (281)
43 standard gamble$.ti,ab,kw. (818)
44 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. (1639)

45 (factc or fact-c or factp or fact-p).ti,ab,kw. (305)
46 (PC-QoL or PCQOL or PORPUS or PROSQOLI or PROS-QOLI).ti,ab,kw. (50)
47 (QOLM-P14 or QOLMP14).ti,ab,kw. (4)
48 or/22-47 (72597)
49 *"cost of illness"/ (3418)
50 exp *"health care cost"/ (48801)
51 *"cost"/ (12982)
52 *"cost benefit analysis"/ or *"cost effectiveness analysis"/ or *"cost minimization analysis"/ or *"cost utility analysis"/ (23924)
53 *economic evaluation/ (2741)
54 (cost or costs).ti,ab,kw. (431210)
55 (costing adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kw. (129)
56 (burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kw. (24862)
57 (resource$1 adj4 (use$1 or usage or utilit$)).ti,ab,kw. (24606)
58 (economic evaluation$ or pharmacoeconomic$).ti,ab,kw. (15747)
59 (hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized).ti,ab,kw. (222318)
60 (admission$1 or readmission$1 or admitted or readmitted or visit or visits).ti,ab,kw. (513751)
61 *"length of stay"/ (6006)
62 (bed adj2 days).ti,ab,kw. (2541)
63 hospital stay$1.ti,ab,kw. (74635)
64 ((days or time or length or duration$1) adj3 hospital$).ti,ab,kw. (79114)
65 ((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kw. (87109)
66 ((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kw. (21571)
67 or/49-66 (1202303)
68 48 or 67 (1251519)
69 21 and 68 (2288)
70 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5012481)
71 69 not 70 (2280)
72 (editorial or letter).pt. (1316170)
73 case report.ti. (204700)
74 71 not (72 or 73) (2187)

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 2187

Table D7 Search strategy in Econlit 1886 to September 2014

1 (prostat$ and (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).af. (76) 2 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).af. (1) 3 1 or 2 (77)

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 77

Table D8 Search strategy in NHS Economic Evaluation Database (NHS EED)

1 (MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES IN NHSEED) 133 2 (MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia IN NHSEED) 2 3 ((prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR intra-epithelial*)) IN NHSEED) 172 4 ((mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) IN NHSEED) 1 5 (#1 OR #2 OR #3 OR #4) 172

Interface / URL: http://www.crd.york.ac.uk/crdweb/
Search date: 23/10/14
Retrieved records: 172

Table D9 Search strategy in Health Technology Assessment Database (HTA)

1 (MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES IN HTA) 218 2 (MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia IN HTA) 0 3 ((prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR intra-epithelial*)) IN HTA) 259 4 ((mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) IN HTA) 6 5 (#1 OR #2 OR #3 OR #4) 259

Interface / URL: http://www.crd.york.ac.uk/crdweb/
Search date: 23/10/14
Retrieved records: 259

Table D10 Search strategy for HEED: Health Economic Evaluations Database

S3 S1 or S2 480 S2 TX(mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) 5 S1 TX(prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR "intra-epithelial*")) 480

Interface / URL: EBSCOHost
Search date: 23/10/14
Retrieved records: 480

Table D11 Search strategy for Cost-Effectiveness Analysis (CEA) Registry

1. prostate = 68 results 2. prostatic = 33 3. mCRPC = 0 4. mHRPC = 0 5. mAIPC = 0 6. CRPC = 1 7. HRPC = 2 8. AIPC = 1

Interface / URL: https://research.tufts-nemc.org/cear4/Home.aspx
Search date: 23/10/14
Retrieved records: 12 (105 returned from search and hand-checked against records already retrieved – 12 unique records added to EndNote).
Basic search used at: https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx

Table D12 Search strategy in Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)

Used basic search for the term: 'Genital neoplasms' Retrieved 8 results from which only 6 applied to male: EPIC, PC-QoL, PROSQOLI, QOLM-P14, UCLA-PCI, UCLA-PCI-SF The bibliographic references of each instrument were copied into a Word document and assessed by reviewer. 3 selected for retrieval and added to EndNote

Interface / URL: http://www.proqolid.org/
Search date: 5/11/14
Retrieved records: 3

Table D13 Search strategy in Scottish Medicines Consortium website

Using search box on the homepage, searched on the following search string: prostate prostatic mCRPC mHRPC mAIPC CRPC HRPC AIPC 27 search results were copied into a Word document and assessed by reviewer. 3 selected for retrieval and added to EndNote

Interface / URL: http://www.scottishmedicines.org.uk/Home
Search date: 5/11/14
Retrieved records: 3

Table D14 Search strategy in Pharmaceutical Benefits Advisory Committee (PBAC) - Pharmaceutical Benefits Scheme (PBS) website

Used ‘Search the PBS’ search box from the homepage. ‘Search for Medicines’ search box, searched on following terms: prostate = 0 results prostatic = 0 results mCRPC = 0 results mHRPC = 0 results mAIPC = 0 results CRPC = 0 results HRPC = 0 results AIPC = 0 results ‘Search PBS Info’ search box, searched on following terms: Prostate= 66 results all PBS documents copied into Word and assessed by reviewer. prostatic = 33 results all PBS documents copied into Word and assessed by reviewer 1 record selected for retrieval

Interface / URL: http://www.pbs.gov.au/pbs/home
Search date: 05/11/14
Retrieved records: 1

Table D15 Search strategy in NICE

Navigated to Urogenital Cancer guidance using the following path: Home>Guidance> Conditions and diseases>Cancer>Prostate cancer. One new TA and 9 new in-development documents saved into a Word document and assessed by reviewer 0 records selected for retrieval.

Interface / URL: http://www.nice.org.uk/
Search date: 05/11/14
Retrieved records: 0

Table D16 Search strategy in Pan-Canadian Oncology Drug Review (pCODR)

Searched using ‘Find a review’ tab. Reviews on prostate cancer located using Tumor Type ordering function and navigating to Genitourinary. 3 reviews found only one record new since last search (24/03/2014). Review ‘under review’ saved into a Word document and assessed by reviewer. 0 records selected for retrieval.

Interface / URL: http://www.pcodr.ca/wcpc/portal/
Search date: 05/11/14
Retrieved records: 0

Table D17 Search strategy in Dental and Pharamceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)

enzalutamide = 8 results (7 new since last search 24/03/2014) cabazitaxel = 7 results (4 new since last search 24/03/2014) abiraterone = 5 results (5 since last search 24/03/2014) All results since last search downloaded into a Word document and assessed by reviewer. 4 records selected for retrieval

Interface / URL: http://www.tlv.se/
Search date: 05/11/14
Retrieved records: 4

Table D18 Search strategy in PubMed

#91 Search (#89 NOT #90) 255 #90 Search (#85 NOT (#86 OR #87 OR #88)) Filters: MEDLINE 1949 #89 Search (#85 NOT (#86 OR #87 OR #88)) 2204 #88 Search case report[ti] 165164 #87 Search news[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR case reports[pt] 3022804 #86 Search animals[mh] NOT humans[mh:noexp] 3940729 #85 Search (#29 AND #84) 2489 #84 Search (#72 OR #83) 1201953 #83 Search (#73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82) 1108022 #82 Search (days[ot] OR time[ot] OR length[ot] OR duration*[ot]) AND (hospital*[ot] OR stay[ot] OR stays[ot] OR stayed[ot] OR discharge[ot] OR discharged[ot] OR home[ot] OR homes[ot]) 568 #81 Search (days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (hospital*[tiab] OR stay[tiab] OR stays[tiab] OR stayed[tiab] OR discharge[tiab] OR discharged[tiab] OR home[tiab] OR homes[tiab]) 338995 #80 Search economic evaluation*[tiab] OR pharmacoeconomic*[tiab] OR economic evaluation*[ot] OR pharmacoeconomic*[ot] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR hospitalised[tiab] OR hospitalized[tiab] OR hospitalization*[ot] OR hospitalisation*[ot] OR hospitalised[ot] OR hospitalized[ot] OR admission*[tiab] OR readmission*[tiab] OR admitted[tiab] OR readmitted[tiab] OR visit[tiab] OR visits[tiab] OR admission*[ot] OR readmission*[ot] OR admitted[ot] OR readmitted[ot] OR visit[ot] OR visits[ot] OR hospital stay*[tiab] OR hospital stay*[ot] 515385 #79 Search (resource*[tiab] AND (use*[tiab] OR usage[tiab] OR utilit*[tiab])) OR (resource*[ot] AND (use*[ot] OR usage[ot] OR utilit*[ot])) 25604 #78 Search ((costing[tiab] OR burden*[tiab]) AND (illness*[tiab] OR disease*[tiab] OR sickness*[tiab] OR treatment*[tiab] OR therap*[tiab])) OR ((costing[ot] OR burden*[ot]) AND (illness*[ot] OR disease*[ot] OR sickness*[ot] OR treatment*[ot] OR

therap*[ot])) 69012
#77 Search cost[tiab] OR costs[tiab] OR cost[ot] OR costs[ot] 336102
#76 Search "Cost-Benefit Analysis"[Mesh:NoExp] 60035
#75 Search "Costs and Cost Analysis"[Mesh:NoExp] 41684
#74 Search "Health Care Costs"[Mesh] 46713
#73 Search "Cost of Illness"[Mesh:NoExp] 17841
#72 Search (#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71) 124150
#71 Search PC-QoL[tiab] OR PCQOL[tiab] OR PORPUS[tiab] OR PROSQOLI[tiab] OR PROS-QOLI[tiab] OR QOLM-P14[tiab] OR QOLMP14[tiab] OR PC-QoL[ot] OR PCQOL[ot] OR PORPUS[ot] OR PROSQOLI[ot] OR PROS-QOLI[ot] OR QOLM-P14[ot] OR QOLMP14[ot] 41
#70 Search factc[ot] OR fact-c[ot] OR factp[ot] OR fact-p[ot] 1
#69 Search factc[tiab] OR fact-c[tiab] OR factp[tiab] OR fact-p[tiab] 140
#68 Search time trade off*[ot] OR time tradeoff*[ot] OR tto[ot] OR timetradeoff*[ot] 31
#67 Search time trade off*[tiab] OR time tradeoff*[tiab] OR tto[tiab] OR timetradeoff*[tiab] 1253
#66 Search standard gamble*[tiab] OR standard gamble*[ot] 684
#65 Search sf20[tiab] OR sf 20[tiab] OR sf twenty[tiab] OR sftwenty[tiab] OR sf20[ot] OR sf 20[ot] OR sf twenty[ot] OR sftwenty[ot] 298
#64 Search sf16[tiab] OR sf 16[tiab] OR sf sixteen[tiab] OR sfsixteen[tiab] OR sf16[ot] OR sf 16[ot] OR sf sixteen[ot] OR sfsixteen[ot] 18
#63 Search sf12[ot] OR sf 12[ot] OR sf twelve[ot] OR sftwelve[ot] 43
#62 Search sf12[tiab] OR sf 12[tiab] OR sf twelve[tiab] OR sftwelve[tiab] 2479
#61 Search (SF[tiab] AND six*[tiab]) OR (SF[ot] AND six*[ot]) 3180
#60 Search sf6*[tiab] OR sf 6*[tiab] OR sfsix*[tiab] OR sf8[tiab] OR sf 8[tiab] OR sfeight[tiab] OR sf eight[tiab] OR sf6*[ot] OR sf 6*[ot] OR sfsix*[ot] OR sf8[ot] OR sf 8[ot] OR sfeight[ot] OR sf eight[ot] 2369
#59 Search sf36*[ot] OR sf 36*[ot] OR sf thirtysix[ot] OR sf thirty six[ot] 183
#58 Search sf36*[tiab] OR sf 36*[tiab] OR sf thirtysix[tiab] OR sf thirty six[tiab] 14518
#57 Search short form*[ot] OR shortform*[ot] 133
#56 Search short form*[tiab] OR shortform*[tiab] 18907
#55 Search euro qual[ot] OR euro qol[ot] OR eq-5d[ot] OR eq5-d[ot] OR eq5d[ot] OR euroqual[ot] OR euroqol[ot] OR euroqual5d[ot] OR euroqol5d[ot] OR qual5d[ot] OR qol5d[ot] 117
#54 Search euro qual[tiab] OR euro qol[tiab] OR eq-5d[tiab] OR eq5-d[tiab] OR eq5d[tiab] OR euroqual[tiab] OR euroqol[tiab] OR euroqual5d[tiab] OR euroqol5d[tiab] OR qual5d[tiab] OR qol5d[tiab] 4539
#53 Search illness state*[ot] OR health state*[ot] 258

#52 Search illness state*[tiab] OR health state*[tiab] 3999
#51 Search hui[ot] OR hui1[ot] OR hui2[ot] OR hui3[ot] 9
#50 Search hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] 962
#49 Search hye[tiab] OR hyes[tiab] OR hye[ot] OR hyes[ot] 56
#48 Search health*[ot] AND year*[ot] AND equivalent*[ot] 1
#47 Search health*[tiab] AND year*[tiab] AND equivalent*[tiab] 4523
#46 Search disutility[ot] OR disutilities[ot] 1
#45 Search disutility[tiab] OR disutilities[tiab] 237
#44 Search utilit*[ot] AND (valu*[ot] OR measur*[ot] OR health[ot] OR life[ot] OR estimat*[ot] OR elicit*[ot] OR disease[ot] OR scale*[ot] OR instrument*[ot] OR score*[ot]) 169
#43 Search utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR scale*[tiab] OR instrument*[tiab] OR score*[tiab]) 74182
#42 Search multiattribute*[ot] OR multi attribute*[ot] 13
#41 Search multiattribute*[tiab] OR multi attribute*[tiab] 531
#40 Search (index[ot] AND wellbeing[ot]) OR (quality[ot] AND wellbeing[ot]) OR qwb[ot]11
#39 Search (index[tiab] AND wellbeing[tiab]) OR (quality[tiab] AND wellbeing[tiab]) OR qwb[tiab] 1764
#38 Search daly*[ot] 30
#37 Search daly*[tiab] 1374
#36 Search disability adjusted life[ot] 35
#35 Search disability adjusted life[tiab] 1409
#34 Search qaly*[ot] OR qald*[ot] OR qale*[ot] OR qtime*[ot] 72
#33 Search qaly*[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab] 5525
#32 Search quality adjusted[ot] OR adjusted life year*[ot] 115
#31 Search quality adjusted[tiab] OR adjusted life year*[tiab] 8420
#30 Search "Quality-Adjusted Life Years"[Mesh:NoExp] 6987
#29 Search (#25 OR #26 OR #27 OR #28) 39479
#28 Search "Prostatic Neoplasms, Castration-Resistant"[Mesh:NoExp] 325
#27 Search mCRPC[ot] OR mHRPC[ot] OR mAIPC[ot] OR CRPC[ot] OR HRPC[ot] OR AIPC[ot] 53
#26 Search mCRPC[tiab] OR mHRPC[tiab] OR mAIPC[tiab] OR CRPC[tiab] OR HRPC[tiab] OR AIPC[tiab] 2260
#25 Search (#5 AND #24) 39280
#24 Search (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) 1182969
#23 Search advanced[tiab] OR advanced[ot] 268600
#22 Search stage 4[ot] OR stage4[ot] OR stage IV[ot] OR stageIV[ot] 40
#21 Search stage 4[tiab] OR stage4[tiab] OR stage IV[tiab] OR stageIV[tiab] 19204
#20 Search D1[ot] OR D2[ot] 595
#19 Search D1[tiab] OR D2[tiab] 55944

#18 Search M1[ot] OR M1a[ot] OR M1b[ot] OR M1c[ot] 206
#17 Search M1[tiab] OR M1a[tiab] OR M1b[tiab] OR M1c[tiab] 22910
#16 Search androgen resistan*[ot] OR androgen refractor*[ot] OR androgen relaps*[ot] OR androgen independen*[ot] 30
#15 Search androgen resistan*[tiab] OR androgen refractor*[tiab] OR androgen relaps*[tiab] OR androgen independen*[tiab]4618
#14 Search hormone resistan*[ot] OR hormone refractor*[ot] OR hormone relaps*[ot] OR hormone independen*[ot] 68
#13 Search hormone resistan*[tiab] OR hormone refractor*[tiab] OR hormone relaps*[tiab] OR hormone independen*[tiab] 5275
#12 Search castrat*[ot] AND (resistan*[ot] OR refractor*[ot] OR relaps*[ot] OR independen*[ot]) 245
#11 Search castrat*[tiab] AND (resistan*[tiab] OR refractor*[tiab] OR relaps*[tiab] OR independen*[tiab]) 4440
#10 Search (metastat*[ot] OR meta-stat*[ot] OR metastas*[ot] OR meta-stas*[ot] OR disseminat*[ot] OR spread*[ot] OR migrat*[ot]) 20924
#9 Search metastat*[tiab] OR meta-stat*[tiab] OR metastas*[tiab] OR meta-stas*[tiab] OR disseminat*[tiab] OR spread*[tiab] OR migrat*[tiab] 716783
#8 Search "Drug Resistance, Neoplasm"[Mesh:NoExp]28002
#7 Search "Bone Neoplasms"[Mesh] 101720
#6 Search "Neoplasm Metastasis"[Mesh] 156533
#5 Search (#1 OR #2 OR #3 OR #4) 125763
#4 Search prostat*[ot] AND (cancer*[ot] OR carcin*[ot] OR tumor*[ot] OR tumour*[ot] OR neoplas*[ot] OR adenocarcin*[ot] OR oncol*[ot] OR malignan*[ot] OR intraepithelial*[ot] OR intra-epithelial*[ot]) 6366
#3 Search prostat*[tiab] AND (cancer*[tiab] OR carcin*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplas*[tiab] OR adenocarcin*[tiab] OR oncol*[tiab] OR malignan*[tiab] OR intraepithelial*[tiab] OR intra-epithelial*[tiab]) 110512
#2 Search "Prostatic Intraepithelial Neoplasia"[Mesh:NoExp] 1192
#1 Search "Prostatic Neoplasms"[Mesh:NoExp]92493

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 23/10/14
Retrieved records: 255

Table D19 Search strategy in Canadian Agency for Drugs and Technologies in Health (CADTH)

Using the search facility in the website. Following search carried out:

prostat* mCRPC mHRPC mAIPC CRPC HRPC AIPC

68 results returned sorted by date of which 43 Publications, 24 Pages, 1 News.
News excluded.
Only retrieved records published since last search (06/05/2014). Only 1 new - excluded for not being relevant to search.

Interface / URL: http://www.cadth.ca/
Search date: 05/11/14
Retrieved records: 0

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.12.6 The inclusion and exclusion criteria.

Table D20 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: • Studies in adults (over the age of 18) with asymptomatic, or mildly symptomatic, mCRPC AND who have not received prior chemotherapy, were eligible for inclusion in the review • Adult patients who have mCRPC, who are pre-progression; • Adult patients who have mCRPC, are asymptomatic and have not undergone chemotherapy; • Adult patients who have mCRPC and have undergone chemotherapy (population is symptomatic) but not final-line treatment of enzalutamide, cabazitaxel or abiraterone; • Adult patients who have mCRPC and undergone chemotherapy and final-line treatment of enzalutamide, cabazitaxel or abiraterone (population is symptomatic). Outcomes: • Health utilities Study design: • Reports of utility elicitation exercises • Reports of utility validation exercises • Reports of economic evaluations using utility measures gathered during the studies Language restrictions • Studies reported in languages other than English were identified and listed for information only
Exclusion criteria	Studies not including all of the following: • Mean or median utility values at different disease levels (if available); • The country/perspective of the study; • A standard method of utility assessment (e.g. standard gamble, time trade-off, rating scale); • A description of the health state valuation instrument (e.g. was a generic preference-based measure such as the EQ-5D used or did they value bespoke health state descriptions).

10.12.7 The data abstraction strategy.

As a minimum, studies selected for further assessment by two reviewers, based on the title and abstract, included information on:

- Patients with mCRPC;
- Utility elicitation, utility validation or report utility elicitation as part of an economic evaluation or review.

The full text of potentially relevant studies were obtained and assessed for relevance by one reviewer and checked by a second reviewer. Discrepancies were resolved through discussion or by consulting a third reviewer.

Studies were data extracted by a health economist and checked by a second researcher. Quality assessment was conducted by one health economist and checked by a second. Any discrepancies were resolved through discussion or by consulting a third researcher.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The databases searched are given in Table D21.

Table D21 Databases searched and provider used for identification of resource utilisation

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
EMBASE	OvidSP
EconLit	OvidSP

NHS Economic Evaluation Database (NHS EED)	http://www.crd.york.ac.uk/crdweb/
Health Economic Evaluation Database (HEED)	EBSCOHost
Cost-Effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4/Home.aspx
Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)	http://www.proqolid.org/
Health Technology Assessment Database (HTA Database)	http://www.crd.york.ac.uk/crdweb/
Scottish Medicines Consortium (SMC)	http://www.scottishmedicines.org.uk/Home
Pharmaceutical Benefits Advisory Committee (PBAC)	http://www.pbs.gov.au/pbs/home
NICE	http://www.nice.org.uk/
Pan-Canadian Oncology Drug Review (pCODR)	http://www.pcodr.ca/wcpc/portal/
Canadian Agency for Drugs and Technologies in Health (CADTH);	http://www.cadth.ca/en
Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)	http://www.tlv.se/

10.13.2 The date on which the search was conducted.

All searches were conducted on October 23, 2014.

10.13.3 The date span of the search.

No time restrictions were applied.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies used to identify studies providing health resource utilisation are provided in Table D22 to Table D36.

Table D22 Search strategy in MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) 1946 to Present

1 Prostatic Neoplasms/ (98481) 2 Prostatic Intraepithelial Neoplasia/ (1293) 3 (prostat$ adj3 (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).ti,ab,kf. (104272)

4 or/1-3 (121891)
5 exp Neoplasm Metastasis/ (162244)
6 exp Bone Neoplasms/ (104098)
7 Drug Resistance, Neoplasm/ (30442)
8 (metastat$ or meta-stat$ or metastas$ or meta-stas$ or disseminat$ or spread$ or migrat$).ti,ab,kf. (736636)
9 (castrat$ and (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (4762)
10 (hormone$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (5529)
11 (androgen$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kf. (3922)
12 (M1 or M1a or M1b or M1c).ti,ab,kf. (23693)
13 (D1 or D2).ti,ab,kf. (57638)
14 ("stage 4" or "stage4" or stage IV or stageIV).ti,ab,kf. (19456)
15 advanced.ti,ab,kf. (273606)
16 or/5-15 (1207912)
17 4 and 16 (38741)
18 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).ti,ab,kf. (2391)
19 Prostatic Neoplasms, Castration-Resistant/ (373)
20 17 or 18 or 19 (38949)
21 Quality-Adjusted Life Years/ (7551)
22 (quality adjusted or adjusted life year$).ti,ab,kf. (8894)
23 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (5821)
24 disability adjusted life.ti,ab,kf. (1452)
25 daly$1.ti,ab,kf. (1379)
26 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf. (401)
27 (multiattribute$ or multi attribute$).ti,ab,kf. (536)
28 (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or scale$1 or instrument$1 or score$1)).ti,ab,kf. (7953)
29 (disutility or disutilities).ti,ab,kf. (255)
30 health$1 year$1 equivalent$1.ti,ab,kf. (40)
31 (hye or hyes).ti,ab,kf. (57)
32 (hui or hui1 or hui2 or hui3).ti,ab,kf. (993)
33 (illness state$1 or health state$1).ti,ab,kf. (4151)
34 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf. (4633)
35 (short form$ or shortform$).ti,ab,kf. (19611)
36 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (15037)
37 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf. (2363)
38 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (2554)
39 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf. (19)
40 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf. (314)
41 standard gamble$.ti,ab,kf. (710)
42 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1279)

43 (factc or fact-c or factp or fact-p).ti,ab,kf. (174)
44 (PC-QoL or PCQOL or PORPUS or PROSQOLI or PROS-QOLI).ti,ab,kf. (37)
45 (QOLM-P14 or QOLMP14).ti,ab,kf. (1)
46 or/21-45 (55644)
47 "cost of illness"/ (18844)
48 exp health care costs/ (48865)
49 "Costs and Cost Analysis"/ (42927)
50 cost-benefit analysis/ (62786)
51 (cost or costs).ti,ab,kf. (340479)
52 (costing adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf. (100)
53 (burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kf. (18411)
54 (resource$1 adj4 (use$1 or usage or utilit$)).ti,ab,kf. (19098)
55 (economic evaluation$ or pharmacoeconomic$).ti,ab,kf. (10380)
56 (hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized).ti,ab,kf. (159076)
57 (admission$1 or readmission$1 or admitted or readmitted or visit or visits).ti,ab,kf. (362379)
58 (bed adj2 days).ti,ab,kf. (1810)
59 hospital stay$1.ti,ab,kf. (51559)
60 ((days or time or length or duration$1) adj3 hospital$).ti,ab,kf. (54832)
61 ((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kf. (57498)
62 ((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kf. (14436)
63 or/47-62 (931325)
64 46 or 63 (968972)
65 20 and 64 (1473)
66 exp animals/ not humans/ (4079856)
67 65 not 66 (1469)
68 (news or comment or editorial or letter or case reports).pt. (3104316)
69 case report.ti. (165536)
70 67 not (68 or 69) (1275)
71 remove duplicates from 70 (1204)

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 1204

Table D23 Search strategy in Embase 1974 to 2014 October 22

1 exp *prostate tumor/ (108202)
2 (prostat$ adj3 (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).ti,ab,kw. (134058)

3 1 or 2 (146427)
4 *metastasis/ (54275)
5 *drug resistance/ (27795)
6 (metastat$ or meta-stat$ or metastas$ or meta-stas$ or disseminat$ or spread$ or migrat$).ti,ab,kw. (892767)
7 (castrat$ and (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (7086)
8 *hormone resistance/ (930)
9 (hormone$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (6742)
10 (androgen$ adj (resistan$ or refractor$ or relaps$ or independen$)).ti,ab,kw. (4567)
11 (M1 or M1a or M1b or M1c).ti,ab,kw. (30583)
12 (D1 or D2).ti,ab,kw. (73341)
13 ("stage 4" or "stage4" or stage IV or stageIV).ti,ab,kw. (28707)
14 *advanced cancer/ (15079)
15 advanced.ti,ab,kw. (361423)
16 or/4-15 (1345291)
17 3 and 16 (46249)
18 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).ti,ab,kw. (4342)
19 *castration resistant prostate cancer/ (2441)
20 exp *prostate tumor/dr (865)
21 17 or 18 or 19 or 20 (46774)
22 *quality adjusted life year/ (802)
23 (quality adjusted or adjusted life year$).ti,ab,kw. (11422)
24 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. (9364)
25 disability adjusted life.ti,ab,kw. (1630)
26 daly$1.ti,ab,kw. (1734)
27 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kw. (571)
28 (multiattribute$ or multi attribute$).ti,ab,kw. (665)
29 (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or scale$1 or instrument$1 or score$1)).ti,ab,kw. (10726)
30 (disutility or disutilities).ti,ab,kw. (391)
31 health$1 year$1 equivalent$1.ti,ab,kw. (42)
32 (hye or hyes).ti,ab,kw. (99)
33 (hui or hui1 or hui2 or hui3).ti,ab,kw. (1356)
34 (illness state$1 or health state$1).ti,ab,kw. (5976)
35 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw. (7533)
36 *short form 12/ or *short form 20/ or *short form 36/ or *short form 8/ or *short form 6D/ (547)
37 (short form$ or shortform$).ti,ab,kw. (23524)
38 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. (21836)
39 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kw. (2938)

40 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw. (3912)
41 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kw. (31)
42 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kw. (281)
43 standard gamble$.ti,ab,kw. (818)
44 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. (1639)
45 (factc or fact-c or factp or fact-p).ti,ab,kw. (305)
46 (PC-QoL or PCQOL or PORPUS or PROSQOLI or PROS-QOLI).ti,ab,kw. (50)
47 (QOLM-P14 or QOLMP14).ti,ab,kw. (4)
48 or/22-47 (72597)
49 *"cost of illness"/ (3418)
50 exp *"health care cost"/ (48801)
51 *"cost"/ (12982)
52 *"cost benefit analysis"/ or *"cost effectiveness analysis"/ or *"cost minimization analysis"/ or *"cost utility analysis"/ (23924)
53 *economic evaluation/ (2741)
54 (cost or costs).ti,ab,kw. (431210)
55 (costing adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kw. (129)
56 (burden$1 adj3 (illness$ or disease$ or sickness$ or treatment$ or therap$)).ti,ab,kw. (24862)
57 (resource$1 adj4 (use$1 or usage or utilit$)).ti,ab,kw. (24606)
58 (economic evaluation$ or pharmacoeconomic$).ti,ab,kw. (15747)
59 (hospitalization$1 or hospitalisation$1 or hospitalised or hospitalized).ti,ab,kw. (222318)
60 (admission$1 or readmission$1 or admitted or readmitted or visit or visits).ti,ab,kw. (513751)
61 *"length of stay"/ (6006)
62 (bed adj2 days).ti,ab,kw. (2541)
63 hospital stay$1.ti,ab,kw. (74635)
64 ((days or time or length or duration$1) adj3 hospital$).ti,ab,kw. (79114)
65 ((days or time or length or duration$1) adj3 (stay or stays or stayed)).ti,ab,kw. (87109)
66 ((days or time or length or duration$1) adj3 (discharge or discharged or home or homes)).ti,ab,kw. (21571)
67 or/49-66 (1202303)
68 48 or 67 (1251519)
69 21 and 68 (2288)
70 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5012481)
71 69 not 70 (2280)
72 (editorial or letter).pt. (1316170)
73 case report.ti. (204700)
74 71 not (72 or 73) (2187)

Interface / URL: OvidSP
Search date: 23/10/14

Retrieved records: 2187

Table D24 Search string in Econlit 1886 to September 2014

1 (prostat$ and (cancer$ or carcin$ or tumor$ or tumour$ or neoplas$ or adenocarcin$ or oncol$ or malignan$ or intraepithelial$ or intra-epithelial$)).af. (76)
2 (mCRPC or mHRPC or mAIPC or CRPC or HRPC or AIPC).af. (1)
3 1 or 2 (77)

Interface / URL: OvidSP
Search date: 23/10/14
Retrieved records: 77

Table D25 Search strategy in NHS Economic Evaluation Database (NHS EED)

1 (MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES IN NHSEED) 133
2 (MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia IN NHSEED) 2
3 ((prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR intra-epithelial*)) IN NHSEED) 172
4 ((mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) IN NHSEED) 1
5 (#1 OR #2 OR #3 OR #4) 172

Interface / URL: http://www.crd.york.ac.uk/crdweb/
Search date: 23/10/14
Retrieved records: 172

Table D26 Search strategy in Health Technology Assessment Database (HTA)

1 (MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES IN HTA) 218
2 (MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia IN HTA) 0
3 ((prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR intra-epithelial*)) IN HTA) 259
4 ((mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) IN HTA) 6
5 (#1 OR #2 OR #3 OR #4) 259

Interface / URL: http://www.crd.york.ac.uk/crdweb/
Search date: 23/10/14
Retrieved records: 259

Table D27 Search strategy in HEED: Health Economic Evaluations Database

S3 S1 or S2 480
S2 TX(mCRPC OR mHRPC OR mAIPC OR CRPC OR HRPC OR AIPC) 5
S1 TX(prostat* AND (cancer* OR carcin* OR tumor* OR tumour* OR neoplas* OR adenocarcin* OR oncol* OR malignan* OR intraepithelial* OR "intra-epithelial*"))

480

Interface / URL: EBSCOHost
Search date: 23/10/14
Retrieved records: 480

Table D28 Search strategy in Cost-Effectiveness Analysis (CEA) Registry

1. prostate = 68 results 2. prostatic = 33 3. mCRPC = 0 4. mHRPC = 0 5. mAIPC = 0 6. CRPC = 1 7. HRPC = 2 8. AIPC = 1

Interface / URL: https://research.tufts-nemc.org/cear4/Home.aspx
Search date: 23/10/14
Retrieved records: 12 (105 returned from search and hand-checked against records already retrieved – 12 unique records added to EndNote).
Basic search used at: https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx

Table D29 Search strategy in Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)

Used basic search for the term: 'Genital neoplasms' Retrieved 8 results from which only 6 applied to male: EPIC, PC-QoL, PROSQOLI, QOLM-P14, UCLA-PCI, UCLA-PCI-SF The bibliographic references of each instrument were copied into a Word document and assessed by reviewer. 3 selected for retrieval and added to EndNote

Interface / URL: http://www.proqolid.org/
Search date: 5/11/14
Retrieved records: 3

Table D30 Search strategy in Scottish Medicines Consortium website

Using search box on the homepage, searched on the following search string: prostate prostatic mCRPC mHRPC mAIPC CRPC HRPC AIPC 27 search results were copied into a Word document and assessed by reviewer. 3 selected for retrieval and added to EndNote

Interface / URL: http://www.scottishmedicines.org.uk/Home
Search date: 5/11/14
Retrieved records: 3

Table D31 Search strategy in Pharmaceutical Benefits Advisory Committee (PBAC) - Pharmaceutical Benefits Scheme (PBS) website

Used 'Search the PBS' search box from the homepage. 'Search for Medicines' search box, searched on following terms: prostate = 0 results prostatic = 0 results mCRPC = 0 results mHRPC = 0 results mAIPC = 0 results CRPC = 0 results HRPC = 0 results AIPC = 0 results 'Search PBS Info' search box, searched on following terms: Prostate= 66 results all PBS documents copied into Word and assessed by reviewer. prostatic = 33 results all PBS documents copied into Word and assessed by reviewer 1 record selected for retrieval

Interface / URL: http://www.pbs.gov.au/pbs/home
Search date: 05/11/14
Retrieved records: 1

Table D32 Search strategy in NICE

Navigated to Urogenital Cancer guidance using the following path: Home>Guidance> Conditions and diseases>Cancer>Prostate cancer. One new TA and 9 new in-development documents saved into a Word document and assessed by reviewer 0 records selected for retrieval.

Interface / URL: http://www.nice.org.uk/
Search date: 05/11/14
Retrieved records: 0

Table D33 Search strategy in Pan-Canadian Oncology Drug Review (pCODR)

Searched using 'Find a review' tab. Reviews on prostate cancer located using Tumor Type ordering function and navigating to Genitourinary. 3 reviews found only one record new since last search (24/03/2014). Review 'under review' saved into a Word document and assessed by reviewer. 0

records selected for retrieval.

Interface / URL: http://www.pcodr.ca/wcpc/portal/
Search date: 05/11/14
Retrieved records: 0

Table D34 Search strategy in Dental and Pharamceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket) (TLV)

Using site search facility and sorting results by date carried out searches on the following terms: enzalutamide = 8 results (7 new since last search 24/03/2014) cabazitaxel = 7 results (4 new since last search 24/03/2014) abiraterone = 5 results (5 since last search 24/03/2014) All results since last search downloaded into a Word document and assessed by reviewer. 4 records selected for retrieval

Interface / URL: http://www.tlv.se/
Search date: 05/11/14
Retrieved records: 4

Table D35 Search strategy in PubMed

#91 Search (#89 NOT #90) 255 #90 Search (#85 NOT (#86 OR #87 OR #88)) Filters: MEDLINE 1949 #89 Search (#85 NOT (#86 OR #87 OR #88)) 2204 #88 Search case report[ti] 165164 #87 Search news[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR case reports[pt] 3022804 #86 Search animals[mh] NOT humans[mh:noexp] 3940729 #85 Search (#29 AND #84) 2489 #84 Search (#72 OR #83) 1201953 #83 Search (#73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82) 1108022 #82 Search (days[ot] OR time[ot] OR length[ot] OR duration*[ot]) AND (hospital*[ot] OR stay[ot] OR stays[ot] OR stayed[ot] OR discharge[ot] OR discharged[ot] OR home[ot] OR homes[ot]) 568 #81 Search (days[tiab] OR time[tiab] OR length[tiab] OR duration*[tiab]) AND (hospital*[tiab] OR stay[tiab] OR stays[tiab] OR stayed[tiab] OR discharge[tiab] OR discharged[tiab] OR home[tiab] OR homes[tiab]) 338995 #80 Search economic evaluation*[tiab] OR pharmacoeconomic*[tiab] OR economic evaluation*[ot] OR pharmacoeconomic*[ot] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR hospitalised[tiab] OR hospitalized[tiab] OR hospitalization*[ot] OR hospitalisation*[ot] OR hospitalised[ot] OR hospitalized[ot] OR admission*[tiab] OR readmission*[tiab] OR admitted[tiab] OR readmitted[tiab] OR

visit[tiab] OR visits[tiab] OR admission*[ot] OR readmission*[ot] OR admitted[ot] OR readmitted[ot] OR visit[ot] OR visits[ot] OR hospital stay*[tiab] OR hospital stay*[ot] 515385

#79 Search (resource*[tiab] AND (use*[tiab] OR usage[tiab] OR utilit*[tiab])) OR (resource*[ot] AND (use*[ot] OR usage[ot] OR utilit*[ot])) 25604

#78 Search ((costing[tiab] OR burden*[tiab]) AND (illness*[tiab] OR disease*[tiab] OR sickness*[tiab] OR treatment*[tiab] OR therap*[tiab])) OR ((costing[ot] OR burden*[ot]) AND (illness*[ot] OR disease*[ot] OR sickness*[ot] OR treatment*[ot] OR therap*[ot])) 69012

#77 Search cost[tiab] OR costs[tiab] OR cost[ot] OR costs[ot] 336102

#76 Search "Cost-Benefit Analysis"[Mesh:NoExp] 60035

#75 Search "Costs and Cost Analysis"[Mesh:NoExp] 41684

#74 Search "Health Care Costs"[Mesh] 46713

#73 Search "Cost of Illness"[Mesh:NoExp] 17841

#72 Search (#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71) 124150

#71 Search PC-QoL[tiab] OR PCQOL[tiab] OR PORPUS[tiab] OR PROSQOLI[tiab] OR PROS-QOLI[tiab] OR QOLM-P14[tiab] OR QOLMP14[tiab] OR PC-QoL[ot] OR PCQOL[ot] OR PORPUS[ot] OR PROSQOLI[ot] OR PROS-QOLI[ot] OR QOLM-P14[ot] OR QOLMP14[ot] 41

#70 Search factc[ot] OR fact-c[ot] OR factp[ot] OR fact-p[ot] 1

#69 Search factc[tiab] OR fact-c[tiab] OR factp[tiab] OR fact-p[tiab] 140

#68 Search time trade off*[ot] OR time tradeoff*[ot] OR tto[ot] OR timetradeoff*[ot] 31

#67 Search time trade off*[tiab] OR time tradeoff*[tiab] OR tto[tiab] OR timetradeoff*[tiab] 1253

#66 Search standard gamble*[tiab] OR standard gamble*[ot] 684

#65 Search sf20[tiab] OR sf 20[tiab] OR sf twenty[tiab] OR sftwenty[tiab] OR sf20[ot] OR sf 20[ot] OR sf twenty[ot] OR sftwenty[ot] 298

#64 Search sf16[tiab] OR sf 16[tiab] OR sf sixteen[tiab] OR sfsixteen[tiab] OR sf16[ot] OR sf 16[ot] OR sf sixteen[ot] OR sfsixteen[ot] 18

#63 Search sf12[ot] OR sf 12[ot] OR sf twelve[ot] OR sftwelve[ot] 43

#62 Search sf12[tiab] OR sf 12[tiab] OR sf twelve[tiab] OR sftwelve[tiab] 2479

#61 Search (SF[tiab] AND six*[tiab]) OR (SF[ot] AND six*[ot]) 3180

#60 Search sf6*[tiab] OR sf 6*[tiab] OR sfsix*[tiab] OR sf8[tiab] OR sf 8[tiab] OR sfeight[tiab] OR sf eight[tiab] OR sf6*[ot] OR sf 6*[ot] OR sfsix*[ot] OR sf8[ot] OR sf 8[ot] OR sfeight[ot] OR sf eight[ot] 2369

#59 Search sf36*[ot] OR sf 36*[ot] OR sf thirtysix[ot] OR sf thirty six[ot] 183

#58 Search sf36*[tiab] OR sf 36*[tiab] OR sf thirtysix[tiab] OR sf thirty six[tiab] 14518

#57 Search short form*[ot] OR shortform*[ot] 133

#56 Search short form*[tiab] OR shortform*[tiab] 18907
#55 Search euro qual[ot] OR euro qol[ot] OR eq-5d[ot] OR eq5-d[ot] OR eq5d[ot] OR euroqual[ot] OR euroqol[ot] OR euroqual5d[ot] OR euroqol5d[ot] OR qual5d[ot] OR qol5d[ot] 117
#54 Search euro qual[tiab] OR euro qol[tiab] OR eq-5d[tiab] OR eq5-d[tiab] OR eq5d[tiab] OR euroqual[tiab] OR euroqol[tiab] OR euroqual5d[tiab] OR euroqol5d[tiab] OR qual5d[tiab] OR qol5d[tiab] 4539
#53 Search illness state*[ot] OR health state*[ot] 258
#52 Search illness state*[tiab] OR health state*[tiab] 3999
#51 Search hui[ot] OR hui1[ot] OR hui2[ot] OR hui3[ot] 9
#50 Search hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] 962
#49 Search hye[tiab] OR hyes[tiab] OR hye[ot] OR hyes[ot] 56
#48 Search health*[ot] AND year*[ot] AND equivalent*[ot] 1
#47 Search health*[tiab] AND year*[tiab] AND equivalent*[tiab] 4523
#46 Search disutility[ot] OR disutilities[ot] 1
#45 Search disutility[tiab] OR disutilities[tiab] 237
#44 Search utilit*[ot] AND (valu*[ot] OR measur*[ot] OR health[ot] OR life[ot] OR estimat*[ot] OR elicit*[ot] OR disease[ot] OR scale*[ot] OR instrument*[ot] OR score*[ot]) 169
#43 Search utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR scale*[tiab] OR instrument*[tiab] OR score*[tiab]) 74182
#42 Search multiattribute*[ot] OR multi attribute*[ot] 13
#41 Search multiattribute*[tiab] OR multi attribute*[tiab] 531
#40 Search (index[ot] AND wellbeing[ot]) OR (quality[ot] AND wellbeing[ot]) OR qwb[ot] 11
#39 Search (index[tiab] AND wellbeing[tiab]) OR (quality[tiab] AND wellbeing[tiab]) OR qwb[tiab] 1764
#38 Search daly*[ot] 30
#37 Search daly*[tiab] 1374
#36 Search disability adjusted life[ot] 35
#35 Search disability adjusted life[tiab] 1409
#34 Search qaly*[ot] OR qald*[ot] OR qale*[ot] OR qtime*[ot] 72
#33 Search qaly*[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab] 5525
#32 Search quality adjusted[ot] OR adjusted life year*[ot] 115
#31 Search quality adjusted[tiab] OR adjusted life year*[tiab] 8420
#30 Search "Quality-Adjusted Life Years"[Mesh:NoExp] 6987
#29 Search (#25 OR #26 OR #27 OR #28) 39479
#28 Search "Prostatic Neoplasms, Castration-Resistant"[Mesh:NoExp] 325
#27 Search mCRPC[ot] OR mHRPC[ot] OR mAIPC[ot] OR CRPC[ot] OR HRPC[ot] OR AIPC[ot] 53
#26 Search mCRPC[tiab] OR mHRPC[tiab] OR mAIPC[tiab] OR CRPC[tiab] OR HRPC[tiab] OR AIPC[tiab] 2260
#25 Search (#5 AND #24) 39280
#24 Search (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) 1182969
#23 Search advanced[tiab] OR advanced[ot] 268600
#22 Search stage 4[ot] OR stage4[ot] OR stage IV[ot] OR stageIV[ot] 40
#21 Search stage 4[tiab] OR stage4[tiab] OR stage IV[tiab] OR stageIV[tiab] 19204
#20 Search D1[ot] OR D2[ot] 595
#19 Search D1[tiab] OR D2[tiab] 55944
#18 Search M1[ot] OR M1a[ot] OR M1b[ot] OR M1c[ot] 206
#17 Search M1[tiab] OR M1a[tiab] OR M1b[tiab] OR M1c[tiab] 22910
#16 Search androgen resistan*[ot] OR androgen refractor*[ot] OR androgen relaps*[ot] OR androgen independen*[ot] 30
#15 Search androgen resistan*[tiab] OR androgen refractor*[tiab] OR androgen relaps*[tiab] OR androgen independen*[tiab]4618
#14 Search hormone resistan*[ot] OR hormone refractor*[ot] OR hormone relaps*[ot] OR hormone independen*[ot] 68
#13 Search hormone resistan*[tiab] OR hormone refractor*[tiab] OR hormone relaps*[tiab] OR hormone independen*[tiab] 5275
#12 Search castrat*[ot] AND (resistan*[ot] OR refractor*[ot] OR relaps*[ot] OR independen*[ot]) 245
#11 Search castrat*[tiab] AND (resistan*[tiab] OR refractor*[tiab] OR relaps*[tiab] OR independen*[tiab]) 4440
#10 Search (metastat*[ot] OR meta-stat*[ot] OR metastas*[ot] OR meta-stas*[ot] OR disseminat*[ot] OR spread*[ot] OR migrat*[ot]) 20924
#9 Search metastat*[tiab] OR meta-stat*[tiab] OR metastas*[tiab] OR meta-stas*[tiab] OR disseminat*[tiab] OR spread*[tiab] OR migrat*[tiab] 716783
#8 Search "Drug Resistance, Neoplasm"[Mesh:NoExp]28002
#7 Search "Bone Neoplasms"[Mesh] 101720
#6 Search "Neoplasm Metastasis"[Mesh] 156533
#5 Search (#1 OR #2 OR #3 OR #4) 125763
#4 Search prostat*[ot] AND (cancer*[ot] OR carcin*[ot] OR tumor*[ot] OR tumour*[ot] OR neoplas*[ot] OR adenocarcin*[ot] OR oncol*[ot] OR malignan*[ot] OR intraepithelial*[ot] OR intra-epithelial*[ot]) 6366
#3 Search prostat*[tiab] AND (cancer*[tiab] OR carcin*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplas*[tiab] OR adenocarcin*[tiab] OR oncol*[tiab] OR malignan*[tiab] OR intraepithelial*[tiab] OR intra-epithelial*[tiab]) 110512
#2 Search "Prostatic Intraepithelial Neoplasia"[Mesh:NoExp] 1192
#1 Search "Prostatic Neoplasms"[Mesh:NoExp]92493

Interface / URL: http://www.ncbi.nlm.nih.gov/pubmed
Search date: 23/10/14
Retrieved records: 255

Table D36 Search strategy in Canadian Agency for Drugs and Technologies in Health (CADTH)

Using the search facility in the website. Following search carried out: prostat* mCRPC mHRPC mAIPC CRPC HRPC AIPC 68 results returned sorted by date of which 43 Publications, 24 Pages, 1 News. News excluded. Only retrieved records published since last search (06/05/2014). Only 1 new - excluded for not being relevant to search.

Interface / URL: http://www.cadth.ca/
Search date: 05/11/14
Retrieved records: 0

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.13.6 The inclusion and exclusion criteria.

Table D37 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: • Studies in adults (over the age of 18) with asymptomatic, or mildly symptomatic, mCRPC AND who have not received prior chemotherapy, were eligible for inclusion in the review • Adult patients who have mCRPC • Adult patients who have mCRPC, are asymptomatic and have not undergone chemotherapy • Adult patients who have mCRPC and have undergone chemotherapy (population is symptomatic) but have not received not final-line treatment of enzalutamide, cabazitaxel or abiraterone • Adult patients who have mCRPC and have undergone chemotherapy and final-line treatment with enzalutamide, cabazitaxel or abiraterone (population is symptomatic) • Adult patients who have mCRPC and are receiving palliative care (no active treatment). Outcomes: • Health resource utilisation Study design: • Studies of any design reporting resource use were eligible for inclusion. Studies published as abstracts or conference presentations, and data from unpublished studies were eligible for inclusion in the review if adequate data were provided. Systematic reviews were eligible for inclusion as a source of references to primary studies. Language restrictions • Studies reported in languages other than English were identified and listed for information only
Exclusion criteria	Studies not including any of the following: • Treatments:

	Clinical effectiveness
	- Type of treatment - Number of treatments - Administration cost • Monitoring costs where applicable - Concomitant medication - Hospital utilisation - Number of hospitalisations - Outpatient visits - Bed days - Staffing - Scans (e.g. computerised tomography (CT) or magnetic resonance imaging (MRI)) • Tests (e.g. ultrasound, electrocardiogram (ECG)) - Lab tests (e.g. full blood count, liver function tests, kidney function tests, prostate-specific antigen (PSA) test) - Accident and Emergency (A&E) visits or other unscheduled visits - Nurse visits - Surgeries and procedures; - Costs. • Other: - GP visits - Hospice/end of life costs.

10.13.7 The data abstraction strategy.

The full text of potentially relevant studies were obtained and assessed for relevance by one reviewer and checked by a second reviewer. Discrepancies were resolved through discussion or by consulting a third reviewer.

Studies were data extracted by a health economist and checked by a second researcher. Quality assessment was conducted by one health economist and checked by a second. Any discrepancies were resolved through discussion or by consulting a third researcher.

10.14 Appendix 14: Parameters varied in one-way SA and their confidence intervals (section 7.6.2)

Table D38 Parameters varied in one-way SA and their confidence intervals

Variable name	Variable description	Model input	LCI	UCI
time_horizon	Time horizon in years	10.00	5	15
r_discount_eff	Discount rate effects	3.5%	0%	5%
r_discount_cost	Discount rate costs	3.5%	0%	5%
patients_receiving_2nd_line_tr_enza_arm	% of progressed patients who receive 2nd line treatment after 1st line enzalutamide	0.84	0%	100%
patients_receiving_2nd_line_tr_WW_arm	% of progressed patients who receive 2nd line treatment after 1st line WW	0.84	0%	100%
patients_receiving_2nd_line_tr_abi_ar	% of progressed patients who receive 2nd	0.84	0%	100%

Variable name	Variable description	Model input	LCI	UCI
m	line treatment after 1st line abiraterone			
patients_receiving_3rd_line_cabazitaxel_or_docet	% of patients moving to 3rd line cabazitaxel or docetaxel after progression of 2nd line treatment	0.81	0%	100%
patients_receiving_3rd_line_enza	% of patients moving to 3rd line enzalutamide after progression of 2nd line treatment	0.81	0%	100%
patients_receiving_3rd_line_abi	% of patients moving to 3rd line abiraterone after progression of 2nd line treatment	0.81	0%	100%
c_Enza	Daily drug costs for enzalutamide	97.67	73.25	122.08
c_Abi	Daily drug costs for abiraterone	97.67	73.25	122.08
c_Docet	Daily drug costs for docetaxel	2.12	1.59	2.65
c_Cabazitaxel	Daily drug costs for cabazitaxel	147.40	110.55	184.25
c_Chemotherapy_Administration	Costs of chemotherapy administration per model cycle	100.80	75.60	125.99
c_health_state_enzalutamide	Health state costs per model cycle for patients on enzalutamide	34.66	28.20	41.78
c_health_state_enzalutamide4plus	Health state costs per model cycle for patients on enzalutamide from month 4	20.91	17.01	25.20
c_health_state_enzalutamide_postchemo	Health state costs per model cycle for patients on enzalutamide given after chemotherapy	24.82	20.20	29.92
c_health_state_abiraterone	Health state costs per model cycle for patients on abiraterone first 3 months	64.55	52.52	77.80
c_health_state_abiraterone4plus	Health state costs per model cycle for patients on abiraterone from month 4	36.26	29.51	43.71
c_health_state_abiraterone_postchemo	Health state costs per model cycle for patients on abiraterone given after chemotherapy	44.48	36.19	53.61
c_health_state_docetaxel	Health state costs per model cycle for patients on docetaxel	73.87	60.10	89.03
c_health_state_palliative	Health state costs per model cycle for patients on palliative treatment	103.82	84.47	125.13
c_health_state_cabazitaxel	Health state costs per model cycle for patients on cabazitaxel	60.01	48.83	72.33
c_health_state_WW	Health state costs per model cycle for patients on WW	36.47	29.68	43.96
c_health_state_PPTF	Health state costs per model cycle for patients in PPTF	36.47	29.68	43.96
c_ConMed_Enzalutamide	Costs of concomitant medications for patients on enza (per cycle)	6.86	5.478	9.049
c_ConMed_abiraterone	Costs of concomitant medications for patients on abi (per cycle)	7.15	5.478	9.049
c_ConMed_docetaxel	Costs of concomitant medications for patients on docetaxel (per cycle)	71.65	54.869	90.645
c_ConMed_palliative	Costs of concomitant medications for patients on palliative therapy (per cycle)	6.93	5.308	8.768
c_ConMed_cabazitaxel	Costs of concomitant medications for patients on cabazitaxel (per cycle)	71.65	54.869	90.645
median_tr_duration_1st_or_2nd_line_docetaxel	Median treatment duration of docetaxel given as 1st or 2nd line	6.58	4.93	8.22
median_tr_duration_2nd_line_enza	Median treatment duration of enzalutamide given as 2nd line	8.30	7.95	9.13
median_tr_duration_2nd_line_abi	Median treatment duration of abiraterone given as 2nd line	7.40	5.55	9.25
median_tr_duration_2nd_line_cabazitaxel	Median treatment duration of cabazitaxel given as 2nd line	4.15	3.12	5.19
median_tr_duration_3nd_line_cabazitaxel	Median treatment duration of cabazitaxel given as 3rd line	4.15	3.12	5.19

Variable name	Variable description	Model input	LCI	UCI
median_tr_duration_3nd_line_enza	Median treatment duration of enzalutamide given as 3rd line	8.30	7.95	9.13
median_tr_duration_3nd_line_abi	Median treatment duration of abiraterone given as 3rd line	7.40	5.55	9.25
median_tr_duration_3nd_line_docetaxel	Median treatment duration of docetaxel given as 3rd line	6.58	4.93	8.22
c_TerminalCare	terminal care costs	3598.00	0	5000
u_Stable_Disease	Utility when on 1st line treatment	0.844	0.836	0.852
u_PPTF	Utility when on watchful waiting	0.720	0.660	0.777
u_Post_Progression1	Utility when on 2nd line treatment	0.658	0.645	0.670
u_Post_Progression2	Utility when on 3rd line treatment	0.612	0.564	0.659
u_Palliative_Care	Utility when on palliative treatment	0.500	0.344	0.656
u_TreatmentGain_Enza	Utility gain for patients on enzalutamide over placebo	0.022	0.003	0.041
u_TreatmentGain_Abi	Utility gain for patients on abiraterone over placebo	0.022	0.003	0.041
u_TreatmentGain_Enza_post_chemo	Utility gain for patients on post-chemo enzalutamide over placebo	0.040	0.032	0.048
int_OS_Enza_Weibull	Intercept of OS Weibull model for enzalutamide Sep 2013 cutoff	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull	Scale of OS Weibull model for enzalutamide Sep 2013 cutoff	[redacted]	[redacted]	[redacted]
int_OS_Enza_Weibull_June_cutoff	Intercept of OS Weibull model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull_June_cutoff	Scale of OS Weibull model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_OS_Enza_LogLogistic_June_cutoff	Intercept of OS LogLogistic model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_OS_Enza_LogLogistic_June_cutoff	Scale of OS LogLogistic model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_OS_PLA_Weibull	Intercept of OS Weibull model for placebo Sep 2013 cutoff	[redacted]	[redacted]	[redacted]
scale_OS_PLA_Weibull	Scale of OS Weibull model for placebo Sep 2013 cutoff	[redacted]	[redacted]	[redacted]
int_OS_PLA_Weibull_June_cutoff	Intercept of OS Weibull model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_OS_PLA_Weibull_June_cutoff	Scale of OS Weibull model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_OS_PLA_LogLogistic_June_cutoff	Intercept of OS LogLogistic model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_OS_PLA_LogLogistic_June_cutoff	Scale of OS LogLogistic model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_OS_Abi_Weibull	Intercept of OS Weibull model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_OS_Abi_Weibull	Scale of OS Weibull model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
int_OS_Abi_LogLog	Intercept of OS Log Logistic model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_OS_Abi_LogLog	Scale of OS Log Logistic model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
int_OS_Abi_Gamma	Intercept of OS Gamma model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_OS_Abi_Gamma	Scale of OS Gamma model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]

Variable name	Variable description	Model input	LCI	UCI
shape_OS_Abi_Gamma	Shape of OS Gamma model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
int_PFS_Enza_Weibull	Intercept of PFS Weibull model for enzalutamide	[redacted]	[redacted]	[redacted]
scale_PFS_Enza_Weibull	Scale of PFS Weibull model for enzalutamide	[redacted]	[redacted]	[redacted]
int_TTD_Enza_Gamma	Intercept of TTD Gamma model for enzalutamide	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_Gamma	Scale of TTD Gamma model for enzalutamide	[redacted]	[redacted]	[redacted]
shape_TTD_Enza_Gamma	Shape of TTD Gamma model for enzalutamide	[redacted]	[redacted]	[redacted]
int_TTD_Enza_Weibull	Intercept of TTD Weibull model for enzalutamide	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_Weibull	Scale of TTD Weibull model for enzalutamide	[redacted]	[redacted]	[redacted]
int_TTD_Enza_Gamma_June_cutoff	Intercept of TTD Gamma model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_Gamma_June_cutoff	Scale of TTD Gamma model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
shape_TTD_Enza_Gamma_June_cutoff	Shape of TTD Gamma model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_TTD_Enza_Weibull_June_cutoff	Intercept of TTD Weibull model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_Weibull_June_cutoff	Scale of TTD Weibull model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_PFS_PLA_Weibull	Intercept of PFS Weibull model for placebo	[redacted]	[redacted]	[redacted]
scale_PFS_PLA_Weibull	Scale of PFS Weibull model for placebo	[redacted]	[redacted]	[redacted]
int_TTD_PLA_Gamma	Intercept of TTD Gamma model for placebo	[redacted]	[redacted]	[redacted]
scale_TTD_PLA_Gamma	Scale of TTD Gamma model for placebo	[redacted]	[redacted]	[redacted]
shape_TTD_PLA_Gamma	Shape of TTD Gamma model for placebo	[redacted]	[redacted]	[redacted]
int_TTD_PLA_Weibull	Intercept of TTD Weibull model for placebo	[redacted]	[redacted]	[redacted]
scale_TTD_PLA_Weibull	Scale of TTD Weibull model for placebo	[redacted]	[redacted]	[redacted]
int_TTD_PLA_Gamma_June_cutoff	Intercept of TTD Gamma model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_PLA_Gamma_June_cutoff	Scale of TTD Gamma model for placebo June cutoff	[redacted]	[redacted]	[redacted]
shape_TTD_PLA_Gamma_June_cutoff	Shape of TTD Gamma model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_TTD_PLA_Weibull_June_cutoff	Intercept of TTD Weibull model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_PLA_Weibull_June_cutoff	Scale of TTD Weibull model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_PFS_Abi_Weibull	Intercept of PFS Weibull model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_PFS_Abi_Weibull	Scale of PFS Weibull model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
int_PFS_Abi_Gamma	Intercept of PFS Gamma model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_PFS_Abi_Gamma	Scale of PFS Gamma model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
shape_PFS_Abi_Gamma	Shape of PFS Gamma model for	[redacted]	[redacted]	[redacted]

Variable name	Variable description	Model input	LCI	UCI
	abiraterone from COU-AA-302 study (IA3)			
int_OS_Enza_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for enzalutamide June cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull_June_cutoff_IPCW	Scale of OS Weibull model for enzalutamide June cutoff IPCW	[redacted]	[redacted]	[redacted]
int_OS_Pla_Weibull_June_cutoff_IPCW	Intercept of OS Weibull model for placebo June cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Pla_Weibull_June_cutoff_IPCW	Scale of OS Weibull model for placebo June cutoff IPCW	[redacted]	[redacted]	[redacted]
int_OS_Enza_Weibull_Sep_two_stage	Intercept of OS Weibull model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull_Sep_two_stage	Scale of OS Weibull model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla_Weibull_Sep_two_stage	Intercept of OS Weibull model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Pla_Weibull_Sep_two_stage	Scale of OS Weibull model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_LogLog_Sep_two_stage	Intercept of OS LogLog model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_LogLog_Sep_two_stage	Scale of OS LogLog model for enzalutamide Sep cutoff IPCW 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla__LogLog_Sep_two_stage	Intercept of OS LogLog model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Pla__LogLog_Sep_two_stage	Scale of OS LogLog model for placebo Sep cutoff IPCW 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_Gamma_Sep_two_stage	Intercept of OS Gamma model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Gamma_Sep_two_stage	Scale of OS Gamma model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
shape_OS_Enza_Gamma_Sep_two_stage	Shape of OS Gamma model for enzalutamide Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla__Gamma_Sep_two_stage	Intercept of OS Gamma model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Pla__Gamma_Sep_two_stage	Scale of OS Gamma model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
shape_OS_Pla__Gamma_Sep_two_stage	Shape of OS Gamma model for placebo Sep cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_Weibull_Sep_IPCW	Intercept of OS Weibull model for enzalutamide Sep cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull_Sep_IPCW	Scale of OS Weibull model for enzalutamide Sep cutoff IPCW	[redacted]	[redacted]	[redacted]
int_OS_Pla_Weibull_Sep_IPCW	Intercept of OS Weibull model for placebo Sep cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Pla_Weibull_Sep_IPCW	Scale of OS Weibull model for placebo Sep cutoff IPCW	[redacted]	[redacted]	[redacted]
int_OS_Enza_Weibull_June_two_stage	Intercept of OS Weibull model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Weibull_June_two_stage	Scale of OS Weibull model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla_Weibull_June_two_stage	Intercept of OS Weibull model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Pla_Weibull_June_two_stage	Scale of OS Weibull model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_LogLog_June_two_stage	Intercept of OS LogLog model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_LogLog_June_two_stage	Scale of OS LogLog model for enzalutamide June cutoff IPCW 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla__LogLog_June_two_stage	Intercept of OS LogLog model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]

Variable name	Variable description	Model input	LCI	UCI
scale_OS_Pla__LogLog_June_two_stage	Scale of OS LogLog model for placebo June cutoff IPCW 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_Gamma_June_two_stage	Intercept of OS Gamma model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Gamma_June_two_stage	Scale of OS Gamma model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
shape_OS_Enza_Gamma_June_two_stage	Shape of OS Gamma model for enzalutamide June cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Pla_Gamma_June_two_stage	Intercept of OS Gamma model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]
scale_OS_Pla_Gamma_June_two_stage	Scale of OS Gamma model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]
shape_OS_Pla_Gamma_June_two_stage	Shape of OS Gamma model for placebo June cutoff 2 stage	[redacted]	[redacted]	[redacted]
int_OS_Enza_Gamma_June_IPCW	Intercept of OS Gamma model for enzalutamide June cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Enza_Gamma_June_IPCW	Scale of OS Gamma model for enzalutamide June cutoff IPCW	[redacted]	[redacted]	[redacted]
shape_OS_Enza_Gamma_June_IPCW	Shape of OS Gamma model for enzalutamide June cutoff IPCW	[redacted]	[redacted]	[redacted]
int_OS_Pla__Gamma_June_IPCW	Intercept of OS Gamma model for placebo June cutoff IPCW	[redacted]	[redacted]	[redacted]
scale_OS_Pla__Gamma_June_IPCW	Scale of OS Gamma model for placebo June cutoff IPCW	[redacted]	[redacted]	[redacted]
shape_OS_Pla__Gamma_June_IPCW	Shape of OS Gamma model for placebo June cutoff IPCW	[redacted]	[redacted]	[redacted]
int_TTD_Enza_LogNormal_June_cutoff	Intercept of TTD LogNormal model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_LogNormal_June_cutoff	Scale of TTD LogNormal model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_TTD_Pla_LogNormal_June_cutoff	Intercept of TTD LogNormal model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Pla_LogNormal_June_cutoff	Scale of TTD LogNormal model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_PFS_Abi_LogNormal	Intercept of PFS LogNormal model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_PFS_Abi_LogNormal	Scale of PFS LogNormal model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
int_TTD_Enza_LogLog_June_cutoff	Intercept of TTD LogNormal model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Enza_LogLog_June_cutoff	Scale of TTD LogLog model for enzalutamide June cutoff	[redacted]	[redacted]	[redacted]
int_TTD_Pla_LogLog_June_cutoff	Intercept of TTD LogLog model for placebo June cutoff	[redacted]	[redacted]	[redacted]
scale_TTD_Pla_LogLog_June_cutoff	Scale of TTD LogLog model for placebo June cutoff	[redacted]	[redacted]	[redacted]
int_PFS_Abi_LogLog	Intercept of PFS LogLog model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
scale_PFS_Abi_LogLog	Scale of PFS LogLog model for abiraterone from COU-AA-302 study (IA3)	[redacted]	[redacted]	[redacted]
HR_OS_Enza_vs_PLA_Sep_cutoff	HR overall survival for enzalutamide vs placebo	[redacted]	[redacted]	[redacted]
HR_OS_Enza_vs_PLA_June_cutoff	HR overall survival for enzalutamide vs Placebo June cutoff	[redacted]	[redacted]	[redacted]
HR_PFS_Enza_vs_PLA	HR PFS for enzalutamide vs placebo	[redacted]	[redacted]	[redacted]
HR_TTD_Enza_vs_PLA	HR TTD for enzalutamide vs placebo	[redacted]	[redacted]	[redacted]

Variable name	Variable description	Model input	LCI	UCI
HR_TTD_Enza_vs_PLA_June_cutoff	HR TTD for enzalutamide vs Placebo June cutoff	[redacted]	[redacted]	[redacted]
HR_OS_Abi_vs_PLA	HR overall survival for abiraterone vs placebo	[redacted]	[redacted]	[redacted]
HR_PFS_Abi_vs_PLA	HR PFS for abiraterone vs placebo	[redacted]	[redacted]	[redacted]
c_AE_abdominal_pain	Cost to treat abdominal pain	699.06	287.18	1290.99
c_AE_anaemia	Cost to treat anaemia	1778.96	802.21	3138.02
c_AE_arthralgia	Cost to treat arthralgia	176.25	55.75	364.87
c_AE_asthenia	Cost to treat asthenia	12.00	4.93	22.16
c_AE_back_pain	Cost to treat back pain	466.66	191.01	863.27
c_AE_bone_pain	Cost to treat bone pain	605.96	220.64	1182.51
c_AE_deterioration_physical_health	Cost to treat deterioration in general physical health	12.00	4.93	22.16
c_AE_diarrhoea	Cost to treat diarrhoea	1944.32	985.31	3223.79
c_AE_fatigue	Cost to treat fatigue	12.00	4.93	22.16
c_AE_febrile_neutropenia	Cost to treat febrile neutropenia	4518.83	1443.21	9318.21
c_AE_haematuria	Cost to treat haematuria	1743.41	776.87	3093.91
c_AE_hypertension	Cost to treat hypertension	432.50	198.93	755.21
c_AE_hypokalaemia	Cost to treat hypokalaemia	347.65	166.16	595.01
c_AE_leukopenia	Cost to treat leukopenia	160.66	15.20	473.46
c_AE_nausea	Cost to treat nausea	1944.32	985.31	3223.79
c_AE_neutropenia	Cost to treat neutropenia	160.66	15.20	473.46
c_AE_oedema_or_peripheral_fluid_retention	Cost to treat oedema/peripheral fluid retention	914.00	375.48	1687.91
c_AE_pain	Cost to treat pain	176.25	55.75	364.87
c_AE_pain_in_extremity	Cost to treat extreme pain	176.25	55.75	364.87
c_AE_thrombocytopaenia	Cost to treat thrombocytopaenia	634.72	223.56	1256.61
c_AE_vomiting	Cost to treat vomiting	1944.32	985.31	3223.79
c_SRE_spinal_cord_compression	Cost to treat spinal cord compression	4687.71	1047.59	11003.11
c_SRE_pathologic_bone_fractures	Cost to treat pathologic bone fractures (non-vertebral)	5351.38	3081.31	8237.73
c_SRE_radiation_to_bone	Cost to treat radiation to bone	682.98	459.49	950.07
c_SRE_surgery_to_bone	Cost to treat surgery to bone	3567.87	1056.26	7580.35
u_AE_abdominal_pain	Disutility associated with abdominal pain	-0.07	-0.093	-0.045
u_AE_anaemia	Disutility associated with anaemia	-0.12	-0.211	-0.027
u_AE_arthralgia	Disutility associated with arthralgia	-0.07	-0.093	-0.045
u_AE_asthenia	Disutility associated with asthenia	-0.13	-0.190	-0.072
u_AE_back_pain	Disutility associated with back pain	-0.07	-0.093	-0.045
u_AE_bone_pain	Disutility associated with bone pain	-0.07	-0.093	-0.045
u_AE_deterioration_physical_health	Disutility associated with deterioration in physical health	-0.13	-0.190	-0.072
u_AE_diarrhoea	Disutility associated with diarrhoea	-0.14	-0.204	-0.070
u_AE_dyspnoea	Disutility associated with dyspnoea	-0.05	-0.074	-0.026
u_AE_fatigue	Disutility associated with fatigue	-0.13	-0.190	-0.072
u_AE_febrile_neutropenia	Disutility associated with febrile neutropenia	-0.12	-0.152	-0.088
u_AE_haematuria	Disutility associated with haematuria	0.00	0.000	0.000
u_AE_hypertension	Disutility associated with hypertension	-0.15	-0.249	-0.057
u_AE_hypokalaemia	Disutility associated with hypokalaemia	0.00	0.000	0.000
u_AE_leukopenia	Disutility associated with leukopenia	-0.09	-0.120	-0.059
u_AE_nausea	Disutility associated with nausea	-0.15	-0.207	-0.096
u_AE_neutropenia	Disutility associated with neutropenia	-0.09	-0.120	-0.059
u_AE_oedema_or_peripheral_fluid_retention	Disutility associated with oedema/peripheral fluid retention	0.00	0.000	0.000
u_AE_pain	Disutility associated with pain	-0.07	-0.093	-0.045
u_AE_pain_in_extremity	Disutility associated with extreme pain	-0.07	-0.093	-0.045

Variable name	Variable description	Model input	LCI	UCI
u_AE_thrombocytopaenia	Disutility associated with thrombocytopaenia	-0.09	-0.120	-0.059
u_AE_vomiting	Disutility associated with vomiting	-0.08	-0.106	-0.045
u_SRE_spinal_cord_compression	Disutility associated with spinal cord compression	-0.24	-0.392	0.000
u_SRE_pathologic_bone_fractures	Disutility associated with pathologic bone fractures (non-vertebral)	-0.20	-0.358	-0.043
u_SRE_radiation_to_bone	Disutility associated with radiation to bone	-0.06	-0.096	-0.015
u_SRE_surgery_to_bone	Disutility associated with surgery to bone	-0.06	-0.096	-0.015
r_AE_abdominal_pain_Enza	Annual AE rate of abdominal pain for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_anaemia_Enza	Annual AE rate of anaemia for patients treated with enzalutamide	0.025	0.0171	0.035
r_AE_arthralgia_Enza	Annual AE rate of arthralgia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_asthenia_Enza	Annual AE rate of asthenia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_back_pain_Enza	Annual AE rate of back pain for patients treated with enzalutamide	0.019	0.0123	0.028
r_AE_bone_pain_Enza	Annual AE rate of bone pain for patients treated with enzalutamide	0.010	0.0058	0.018
r_AE_deteriration_physical_health_Enza	Annual AE rate of deterioration in general physical health for patients treated with enzalutamide	0.015	0.0096	0.024
r_AE_diarrhoea_Enza	Annual AE rate of diarrhoea for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_dyspnoea_Enza	Annual AE rate of dyspnoea for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_fatigue_Enza	Annual AE rate of fatigue for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_febrile_neutropenia_Enza	Annual AE rate of febrile neutropenia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_haematuria_Enza	Annual AE rate of haematuria for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_hypertension_Enza	Annual AE rate of hypertension for patients treated with enzalutamide	0.050	0.0387	0.065
r_AE_hypokalaemia_Enza	Annual AE rate of hypokalaemia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_leukopenia_Enza	Annual AE rate of leukopenia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_nausea_Enza	Annual AE rate of nausea for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_neutropenia_Enza	Annual AE rate of neutropenia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_oedema_or_peripheral_fluid_retention_Enza	Annual AE rate of oedema/peripheral fluid retention for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_pain_Enza	Annual AE rate of pain for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_pain_in_extremity_Enza	Annual AE rate of pain in extremity for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_thrombocytopaenia_Enza	Annual AE rate of thrombocytopaenia for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_vomiting_Enza	Annual AE rate of vomiting for patients treated with enzalutamide	0.000	0.0000	0.000
r_AE_abdominal_pain_BSC	Annual AE rate of abdominal pain for patients treated with BSC	0.000	0.0000	0.000
r_AE_anaemia_BSC	Annual AE rate of anaemia for patients treated with BSC	0.046	0.0312	0.068

Variable name	Variable description	Model input	LCI	UCI
r_AE_arthralgia_BSC	Annual AE rate of arthralgia for patients treated with BSC	0.000	0.0000	0.000
r_AE_asthenia_BSC	Annual AE rate of asthenia for patients treated with BSC	0.000	0.0000	0.000
r_AE_back_pain_BSC	Annual AE rate of back pain for patients treated with BSC	0.046	0.0312	0.068
r_AE_bone_pain_BSC	Annual AE rate of bone pain for patients treated with BSC	0.037	0.0238	0.057
r_AE_deteriration_physical_health_BSC	Annual AE rate of deterioration in general physical health for patients treated with BSC	0.018	0.0099	0.034
r_AE_diarrhoea_BSC	Annual AE rate of diarrhoea for patients treated with BSC	0.000	0.0000	0.000
r_AE_dyspnoea_BSC	Annual AE rate of dyspnoea for patients treated with BSC	0.000	0.0000	0.000
r_AE_fatigue_BSC	Annual AE rate of fatigue for patients treated with BSC	0.000	0.0000	0.000
r_AE_febrile_neutropenia_BSC	Annual AE rate of febrile neutropenia for patients treated with BSC	0.000	0.0000	0.000
r_AE_haematuria_BSC	Annual AE rate of haematuria for patients treated with BSC	0.000	0.0000	0.000
r_AE_hypertension_BSC	Annual AE rate of hypertension for patients treated with BSC	0.035	0.0224	0.055
r_AE_hypokalaemia_BSC	Annual AE rate of hypokalaemia for patients treated with BSC	0.000	0.0000	0.000
r_AE_leukopenia_BSC	Annual AE rate of leukopenia for patients treated with BSC	0.000	0.0000	0.000
r_AE_nausea_BSC	Annual AE rate of nausea for patients treated with BSC	0.000	0.0000	0.000
r_AE_neutropenia_BSC	Annual AE rate of neutropenia for patients treated with BSC	0.000	0.0000	0.000
r_AE_oedema_or_peripheral_fluid_retention_BSC	Annual AE rate of oedema/peripheral fluid retention for patients treated with BSC	0.000	0.0000	0.000
r_AE_pain_BSC	Annual AE rate of pain for patients treated with BSC	0.000	0.0000	0.000
r_AE_pain_in_extremity_BSC	Annual AE rate of pain in extremity for patients treated with BSC	0.000	0.0000	0.000
r_AE_thrombocytopaenia_BSC	Annual AE rate of thrombocytopaenia for patients treated with BSC	0.000	0.0000	0.000
r_AE_vomiting_BSC	Annual AE rate of vomiting for patients treated with BSC	0.000	0.0000	0.000
rd_AE_abdominal_pain_Abi	Rate difference of abdominal pain for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_anaemia_Abi	Rate difference of anaemia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_arthralgia_Abi	Rate difference of arthralgia for patients treated with abiraterone	-0.011	-0.0242	0.002
rd_AE_asthenia_Abi	Rate difference of asthenia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_back_pain_Abi	Rate difference of back pain for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_bone_pain_Abi	Rate difference of bone pain for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_deteriration_physical_health_Abi	Rate difference of deterioration in general physical health for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_diarrhoea_Abi	Rate difference of diarrhoea for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_dyspnoea_Abi	Rate difference of dyspnoea for patients	0.002	-0.0083	0.012

Variable name	Variable description	Model input	LCI	UCI
	treated with abiraterone			
rd_AE_fatigue_Abi	Rate difference of fatigue for patients treated with abiraterone	-0.007	-0.0204	0.005
rd_AE_febrile_neutropenia_Abi	Rate difference of febrile neutropenia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_haematuria_Abi	Rate difference of haematuria for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_hypertension_Abi	Rate difference of hypertension for patients treated with abiraterone	-0.012	-0.0288	0.005
rd_AE_hypokalaemia_Abi	Rate difference of hypokalaemia for patients treated with abiraterone	-0.007	-0.0196	0.006
rd_AE_leukopenia_Abi	Rate difference of leukopenia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_nausea_Abi	Rate difference of nausea for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_neutropenia_Abi	Rate difference of neutropenia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_oedema_ord_peripheral_fluid_retention_Abi	Rate difference of oedema/peripheral fluid retention for patients treated with abiraterone	-0.012	-0.0238	-0.001
rd_AE_pain_Abi	Rate difference of pain for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_pain_in_extremity_Abi	Rate difference of pain in extremity for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_thrombocytopaenia_Abi	Rate difference of thrombocytopaenia for patients treated with abiraterone	0.000	0.0000	0.000
rd_AE_vomiting_Abi	Rate difference of vomiting for patients treated with abiraterone	0.000	0.0000	0.000
r_AE_abdominal_pain_Docet	Annual AE rate of abdominal pain for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_anaemia_Docet	Annual AE rate of anaemia for patients treated with docetaxel	0.093	0.0579	0.150
r_AE_arthralgia_Docet	Annual AE rate of arthralgia for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_asthenia_Docet	Annual AE rate of asthenia for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_back_pain_Docet	Annual AE rate of back pain for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_bone_pain_Docet	Annual AE rate of bone pain for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_deteriration_physical_health_Docet	Annual AE rate of deterioration in general physical health for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_diarrhoea_Docet	Annual AE rate of diarrhoea for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_dyspnoea_Docet	Annual AE rate of dyspnoea for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_fatigue_Docet	Annual AE rate of fatigue for patients treated with docetaxel	0.093	0.0579	0.150
r_AE_febrile_neutropenia_Docet	Annual AE rate of febrile neutropenia for patients treated with docetaxel	0.055	0.0295	0.102
r_AE_haematuria_Docet	Annual AE rate of haematuria for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_hypertension_Docet	Annual AE rate of hypertension for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_hypokalaemia_Docet	Annual AE rate of hypokalaemia for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_leukopenia_Docet	Annual AE rate of leukopenia for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_nausea_Docet	Annual AE rate of nausea for patients	0.000	0.0000	0.000

Variable name	Variable description	Model input	LCI	UCI
	treated with docetaxel			
r_AE_neutropenia_Docet	Annual AE rate of neutropenia for patients treated with docetaxel	0.581	0.4799	0.702
r_AE_oedema_or_peripheral_fluid_retention_Docet	Annual AE rate of oedema/peripheral fluid retention for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_pain_Docet	Annual AE rate of pain for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_pain_in_extremity_Docet	Annual AE rate of extreme pain for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_thrombocytopaenia_Docet	Annual AE rate of thrombocytopaenia for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_vomiting_Docet	Annual AE rate of vomiting for patients treated with docetaxel	0.000	0.0000	0.000
r_AE_abdominal_pain_Cabaz	Annual AE rate of abdominal pain for patients treated with cabazitaxel	0.055	0.0260	0.114
r_AE_anaemia_Cabaz	Annual AE rate of anaemia for patients treated with cabazitaxel	0.304	0.2222	0.416
r_AE_arthralgia_Cabaz	Annual AE rate of arthralgia for patients treated with cabazitaxel	0.031	0.0117	0.083
r_AE_asthenia_Cabaz	Annual AE rate of asthenia for patients treated with cabazitaxel	0.133	0.0824	0.213
r_AE_back_pain_Cabaz	Annual AE rate of back pain for patients treated with cabazitaxel	0.109	0.0646	0.184
r_AE_bone_pain_Cabaz	Annual AE rate of bone pain for patients treated with cabazitaxel	0.023	0.0075	0.073
r_AE_deteriration_physical_health_Cabaz	Annual AE rate of deterioration in general physical health for patients treated with cabazitaxel	0.000	0.0000	0.000
r_AE_diarrhoea_Cabaz	Annual AE rate of diarrhoea for patients treated with cabazitaxel	0.179	0.1192	0.270
r_AE_dyspnoea_Cabaz	Annual AE rate of dyspnoea for patients treated with cabazitaxel	0.039	0.0162	0.094
r_AE_fatigue_Cabaz	Annual AE rate of fatigue for patients treated with cabazitaxel	0.140	0.0884	0.223
r_AE_febrile_neutropenia_Cabaz	Annual AE rate of febrile neutropenia for patients treated with cabazitaxel	0.218	0.1507	0.316
r_AE_haematuria_Cabaz	Annual AE rate of haematuria for patients treated with cabazitaxel	0.055	0.0260	0.114
r_AE_hypertension_Cabaz	Annual AE rate of hypertension for patients treated with cabazitaxel	0.000	0.0000	0.000
r_AE_hypokalaemia_Cabaz	Annual AE rate of hypokalaemia for patients treated with cabazitaxel	0.000	0.0000	0.000
r_AE_leukopenia_Cabaz	Annual AE rate of leukopenia for patients treated with cabazitaxel	1.973	1.7440	2.231
r_AE_nausea_Cabaz	Annual AE rate of nausea for patients treated with cabazitaxel	0.055	0.0260	0.114
r_AE_neutropenia_Cabaz	Annual AE rate of neutropenia for patients treated with cabazitaxel	2.363	2.1109	2.644
r_AE_oedema_or_peripheral_fluid_retention_Cabaz	Annual AE rate of oedema/peripheral fluid retention for patients treated with cabazitaxel	0.000	0.0000	0.000
r_AE_pain_Cabaz	Annual AE rate of pain for patients treated with cabazitaxel	0.031	0.0117	0.083
r_AE_pain_in_extremity_Cabaz	Annual AE rate of pain in extremity for patients treated with cabazitaxel	0.047	0.0210	0.104
r_AE_thrombocytopaenia_Cabaz	Annual AE rate of thrombocytopaenia for patients treated with cabazitaxel	0.117	0.0705	0.194
r_AE_vomiting_Cabaz	Annual AE rate of vomiting for patients treated with cabazitaxel	0.055	0.0260	0.114

Variable name	Variable description	Model input	LCI	UCI
r_SRE_spinal_cord_compression_Enza	Spinal cord compression rate in patients treated with enzalutamide	0.033	0.0241	0.045
r_SRE_pathologic_bone_fractures_Enza	Pathological bone fracture rate in patients treated with enzalutamide	0.036	0.0263	0.048
r_SRE_radiation_to_bone_Enza	Radiation to the bone rate in patients treated with enzalutamide	0.113	0.0952	0.134
r_SRE_surgery_to_bone_Enza	Surgery to the bone rate in patients treated with enzalutamide	0.013	0.0079	0.022
r_SRE_spinal_cord_compression_BSC	Spinal cord compression rate in patients treated with BSC	0.042	0.0277	0.065
r_SRE_pathologic_bone_fractures_BSC	Pathological bone fracture rate in patients treated with BSC	0.030	0.0183	0.050
r_SRE_radiation_to_bone_BSC	Radiation to the bone rate in patients treated with BSC	0.168	0.1352	0.208
r_SRE_surgery_to_bone_BSC	Surgery to the bone rate in patients treated with BSC	0.018	0.0095	0.035
r_SRE_spinal_cord_compression_Abi	Spinal cord compression rate in patients treated with abiraterone	0.033	0.0241	0.045
r_SRE_pathologic_bone_fractures_Abi	Pathological bone fracture rate in patients treated with abiraterone	0.036	0.0263	0.048
r_SRE_radiation_to_bone_Abi	Radiation to the bone rate in patients treated with abiraterone	0.113	0.0952	0.134
r_SRE_surgery_to_bone_Abi	Surgery to the bone rate in patients treated with abiraterone	0.013	0.0079	0.022
rd_SRE_spinal_cord_compression_Abi	Spinal cord compression rate difference abiraterone-placebo	-0.009	-0.0303	0.012
rd_SRE_pathologic_bone_fractures_Abi	Pathological bone fracture rate difference abiraterone-placebo	0.005	-0.0135	0.024
rd_SRE_radiation_to_bone_Abi	Radiation to the bone rate difference abiraterone-placebo	-0.055	-0.0956	-0.014
rd_SRE_surgery_to_bone_Abi	Surgery to the bone rate difference abiraterone-placebo	-0.005	-0.0187	0.008
r_SRE_spinal_cord_compression_Enza_Progressed	Spinal cord compression rate in patients treated with enzalutamide	0.112	0.0966	0.130
r_SRE_pathologic_bone_fractures_Enza_Progressed	Pathological bone fracture rate in patients treated with enzalutamide	0.064	0.0523	0.077
r_SRE_radiation_to_bone_Enza_Progressed	Radiation to the bone rate in patients treated with enzalutamide	0.373	0.3437	0.404
r_SRE_surgery_to_bone_Enza_Progressed	Surgery to the bone rate in patients treated with enzalutamide	0.025	0.0181	0.034
r_SRE_spinal_cord_compression_BSC_Progressed	Spinal cord compression rate in patients treated with BSC	0.112	0.0966	0.130
r_SRE_pathologic_bone_fractures_BSC_Progressed	Pathological bone fracture rate in patients treated with BSC	0.064	0.0523	0.077
r_SRE_radiation_to_bone_BSC_Progressed	Radiation to the bone rate in patients treated with BSC	0.373	0.3437	0.404
r_SRE_surgery_to_bone_BSC_Progressed	Surgery to the bone rate in patients treated with BSC	0.025	0.0181	0.034
r_SRE_spinal_cord_compression_Abi_Progressed	Spinal cord compression rate in patients treated with abiraterone	0.112	0.0966	0.130
r_SRE_pathologic_bone_fractures_Abi_Progressed	Pathological bone fracture rate in patients treated with abiraterone	0.064	0.0523	0.077
r_SRE_radiation_to_bone_Abi_Progressed	Radiation to the bone rate in patients treated with abiraterone	0.373	0.3437	0.404
r_SRE_surgery_to_bone_Abi_Progressed	Surgery to the bone rate in patients treated with abiraterone	0.025	0.0181	0.034
rd_SRE_spinal_cord_compression_Abi_Progressed	Spinal cord compression rate difference abiraterone-placebo	0.112	0.1119	0.112
rd_SRE_pathologic_bone_fractures_Abi_Progressed	Pathological bone fracture rate difference abiraterone-placebo	0.064	0.0636	0.064

Variable name	Variable description	Model input	LCI	UCI
rd_SRE_radiation_to_bone_Abi_Progressed	Radiation to the bone rate difference abiraterone-placebo	0.373	0.3727	0.373
rd_SRE_surgery_to_bone_Abi_Progressed	Surgery to the bone rate difference abiraterone-placebo	0.025	0.0248	0.025
d_AE_abdominal_pain	Duration (days) associated with abdominal pain	10.500	7	14
d_AE_anaemia	Duration (days) associated with anaemia	10.500	7	14
d_AE_arthralgia	Duration (days) associated with arthralgia	10.500	7	14
d_AE_asthenia	Duration (days) associated with asthenia	91.250	21	180
d_AE_back_pain	Duration (days) associated with back pain	10.500	7	14
d_AE_bone_pain	Duration (days) associated with bone pain	10.500	7	14
d_AE_deterioration_physical_health	Duration (days) associated with deterioration in general physical health	91.250	21	180
d_AE_diarrhoea	Duration (days) associated with diarrhoea	10.500	7	14
d_AE_dyspnoea	Duration (days) associated with dyspnoea	10.500	7	14
d_AE_fatigue	Duration (days) associated with fatigue	91.250	21	180
d_AE_febrile_neutropenia	Duration (days) associated with febrile neutropenia	10.500	7	14
d_AE_haematuria	Duration (days) associated with haematuria	10.500	7	14
d_AE_hypertension	Duration (days) associated with hypertension	10.500	7	14
d_AE_hypokalaemia	Duration (days) associated with hypokalaemia	10.500	7	14
d_AE_leukopenia	Duration (days) associated with leukopenia	91.250	21	180
d_AE_nausea	Duration (days) associated with nausea	10.500	7	14
d_AE_neutropenia	Duration (days) associated with neutropenia	10.500	7	14
d_AE_oedema_or_peripheral_fluid_retention	Duration (days) associated with oedema/peripheral fluid retention	10.500	7	14
d_AE_pain	Duration (days) associated with pain	10.500	7	14
d_AE_pain_in_extremity	Duration (days) associated with extreme pain	10.500	7	14
d_AE_thrombocytopaenia	Duration (days) associated with thrombocytopaenia	10.500	7	14
d_AE_vomiting	Duration (days) associated with vomiting	10.500	7	14
d_SRE_spinal_cord_compression	Duration of impact a spinal cord compression on patient's QoL (in days)	30.417	0	213
d_SRE_pathologic_bone_fractures	Duration of impact a pathological bone fracture on patient's QoL (in days)	30.417	0	213
d_SRE_radiation_to_bone	Duration of impact radiation to bone on patient's QoL (in days)	30.417	0	213
d_SRE_surgery_to_bone	Duration of impact surgery to bone on patient's QoL (in days)	30.417	0	213

10.15 Appendix 15: Additional internal reports

10.15.1 Overall survival adjustment for post-study drug treatments in PREVAIL study. Report prepared by Quintiles, 13 January 2015.

Provided in reference pack – reference 37

10.15.2 PREVAIL extrapolation report. Report prepared by Quintiles, 14 January 2015.

Provided in reference pack – reference 81

10.16 Appendix 16: Description of methodology to run scenario analyses

Scenario 1 - Data cut-off September 2013

As more mature survival data is preferred for economic modelling, an updated survival analysis with a data cut-off date of June 30, 2014 was used in the base case model. In this scenario the September data was used to estimate both OS and TTD (section 10.15.2). Similar to the base case, OS was adjusted using the IPCW method. The parametric model was Weibull for OS and Gamma for TTD. All other parameters were unchanged from the base case.

Scenario 2 - Two stage OS adjustment method

As described in section 7.3.1, the IPCW method was deemed most appropriate and is used for the OS adjustment in the model base case. In this scenario the 2 stage method was used for OS adjustment (section 10.15.2). The parametric model was Weibull.

Scenario 3 Unadjusted survival data

As the ITT analysis may underestimate the true difference in clinical benefit of the study drug when the treatment switching takes place, in the model the OS data was adjusted to correct for post-study treatments that are not available in clinical practice. To show the impact of the adjustment on the ICER, an unadjusted analysis was also performed. All parameters were unchanged from their base case values, except for the OS modelling for enzalutamide and BSC. The data cut-off used was June 2014. The parametric model used was Weibull (section 10.15.2).

Scenario 4 Gamma distribution for OS

UK experts selected a Weibull model for the OS due to the more realistic shape of the tail. In this scenario Gamma distribution (which was the best statistical fit for the OS) is used for enzalutamide, placebo and abiraterone arms.

Scenario 5 - Proportional hazards

As a proportionality of hazards assumption did not hold, individual survival curves were applied in the base case model. However, according to PREVAIL, hazard rates were proportional over most of the survival follow-up period. Furthermore, it was considered that the converging of the curves towards the end of the follow-up period was a consequence of the greater proportion of life-extending treatments received by those in the placebo arm of the trial versus those in the enzalutamide arm of the trial. To test the impact of assuming that the hazard rates continued to be proportional until end of follow-up, a scenario assuming proportional hazards was explored. The HR for this scenario is the [redacted] In this scenario TTD for enzalutamide is also modelled by applying a HR [redacted] to the reference curve (BSC).

Scenario 6 - Adjusted indirect comparison for abiraterone OS

As PREVAIL and COU-AA-302 studies had different comparator arms, in the base case abiraterone survival curves were directly applied within the model. In this scenario an adjusted indirect comparison is used for abiraterone's OS. The abiraterone OS HR used in this scenario is 0.79 (0.66; 0.95)[75].

Scenario 7 - rPFS instead of TTD

In the base case TTD is used as the indicator of progression. This is an alternative scenario using rPFS. In this scenario progression for enzalutamide and placebo is modelled using September 2013 rPFS data (Weibull model). As rPFS data are only available for the September cut-off, a second scenario was presented using September TTD (Gamma model) for comparison (section 10.15.2).

Scenario 8 - Weibull distribution for TTD

In the base case TTD is modelled using the Gamma distribution which was selected as a best parametric fit. The Weibull model for TTD was only marginally different from the Gamma. In this scenario Weibull distribution is used to model TTD for enzalutamide, placebo and abiraterone arms.

Scenario 9 - BNF price for docetaxel

In the model the eMit database is used as a source for the docetaxel price (£47.30 per 160mg/8ml solution for infusion vial). In this scenario the BNF price for docetaxel (£1008.54 per 160mg/8ml solution for infusion vial) is used.

Scenario 10 - Including unscheduled costs as per abiraterone submission to NICE

PREVAIL did not capture data on resource utilisation. The abiraterone submission to NICE did include unscheduled resource utilisation, however, as no details of this analysis were presented, there is a limited transparency on the data. For this reason, no unscheduled MRU was included in the base case model. A scenario using data on unscheduled costs from abiraterone submission to NICE was explored. The following costs per month were reported in abiraterone's submission to NICE: £93.79

in progression-free health state and £380.29 in progressed health state. Based on these costs per month, costs per week were calculated and added to the existing health states costs in the model. Costs of AEs and SREs were set to zero to avoid double-counting.

Scenario 11 - Including a 10.36% price rebate as per PPRS agreement for 2015

The 2014 Pharmaceutical Price Regulation Scheme ("PPRS") represented a substantial change from previous price control mechanisms. Under this scheme, overspend on expenditure on branded medicines is repaid to the Department of Health by PPRS member companies. As the PPRS guarantees the NHS budget for medicines, it represents a key factor to be taken into account when assessing whether use of a particular treatment represents good use of NHS resources.

Although NICE has issued no guidance or statement explaining how the PPRS should be taken into account during appraisals, this issue has been discussed during the appeal panel against the final appraisal determination of trastuzumab emtansine for metastatic breast cancer. The appeal panel were persuaded that the PPRS could potentially be relevant to the assessment of opportunity costs that underlies a NICE appraisal.

The 2015 payment percentage is 10.36%, and is expected to further increase to 15% in 2016. However, for the purpose of this scenario, the conservative estimate of 10.36% was used, and applied as a discount to all drug acquisition costs.

Scenario 12 - Increased costs for spinal cord compression

In the model the NHS reference costs 2012-2013 data was used to derive costs for a spinal cord compression (£4,688). UK experts asserted that the spinal cord compression may have higher impact in terms of costs. In this scenario higher costs for the spinal cord compression as per degarelix submission (£10,472) were applied.

Scenario 13 - Abiraterone is given after docetaxel in the BSC arm

Although after docetaxel patients could in clinical practice receive either enzalutamide or abiraterone, for simplicity, the model assumes all patients receive enzalutamide (Table B45). In this scenario abiraterone was given after docetaxel in the BSC arm.

Scenario 14 - Increased duration of SREs

UK experts indicated that SREs may last longer than currently is implemented in the model, therefore the impact of longer SREs was explored in this scenario. An increased duration of SREs from 1 month in the base case to 7 months was applied in this scenario.

Scenario 15 - Baseline utility from AFFIRM is used for PP2 health state

AFFIRM is an alternative source for the PP2 health state utility as the AFFIRM population represents post-docetaxel mHRPC patients. The baseline utility from AFFIRM [redacted] was used for the PP2 health state in this scenario.

Scenario 16 - No disutulity and no costs for AEs

By excluding the impact of AEs, any potential double counting is excluded. In this scenario disutilities and costs for AEs were set to zero.

Scenario 17 - Comparison versus abiraterone while varying its PAS discount in 5% increments and keeping enzalutamide discount to [redacted]

In this scenario enzalutamide's discount was kept constant [redacted] and abiraterone's discount was varied in 5% increment.

10.17 Appendix 17: Extrapolation of the digitised abiraterone's OS and rPFS KM curves from COU-AA-302

Figure D1 Short term overall survival

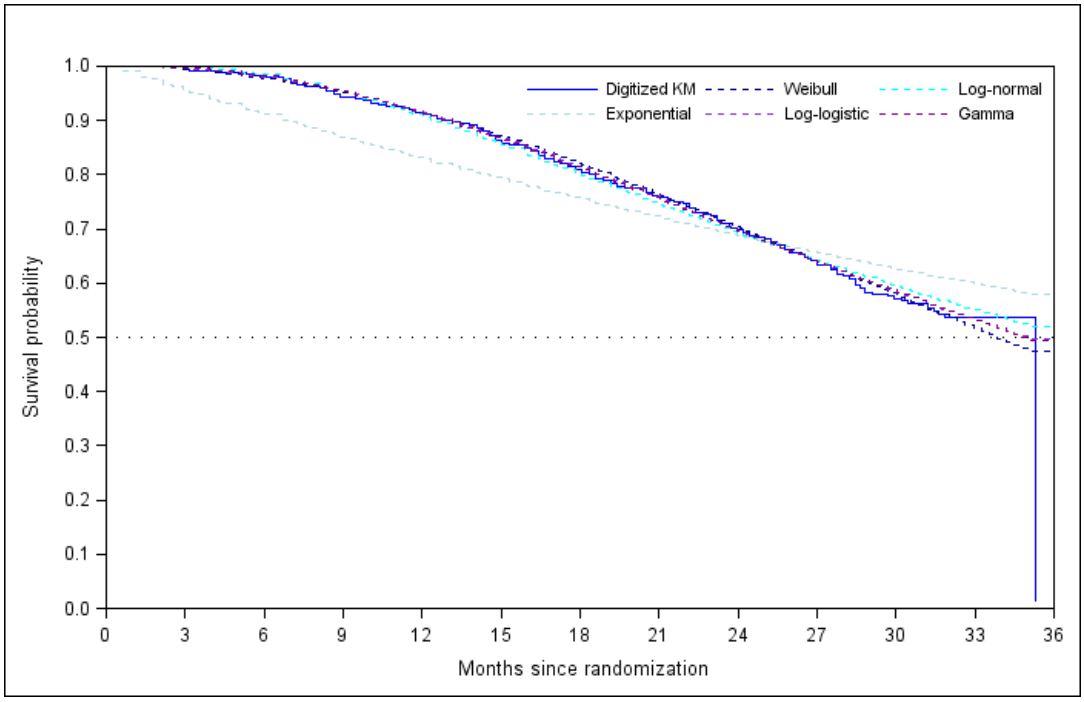


Figure D2 Long term overall survival

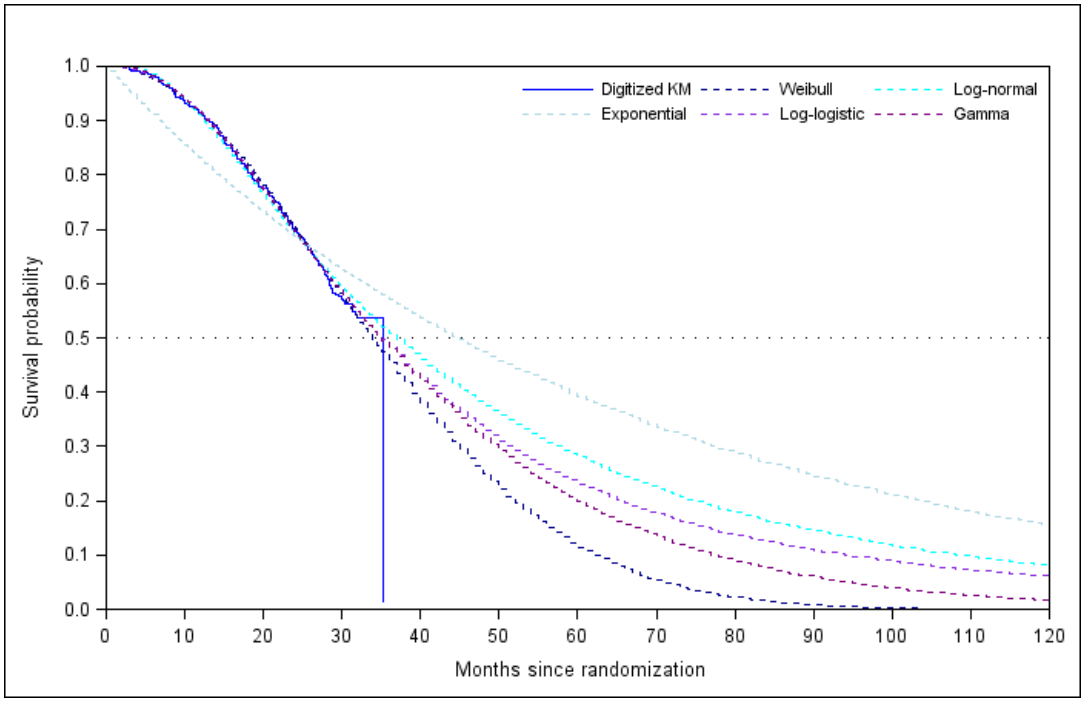


Figure D3 Short term rPFS

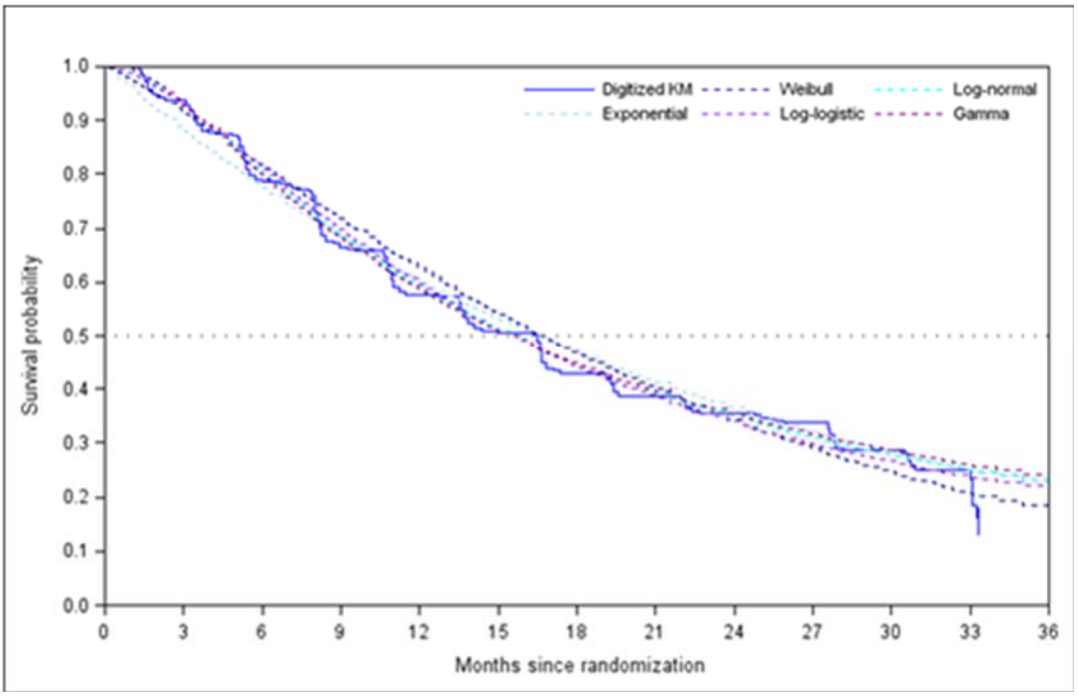
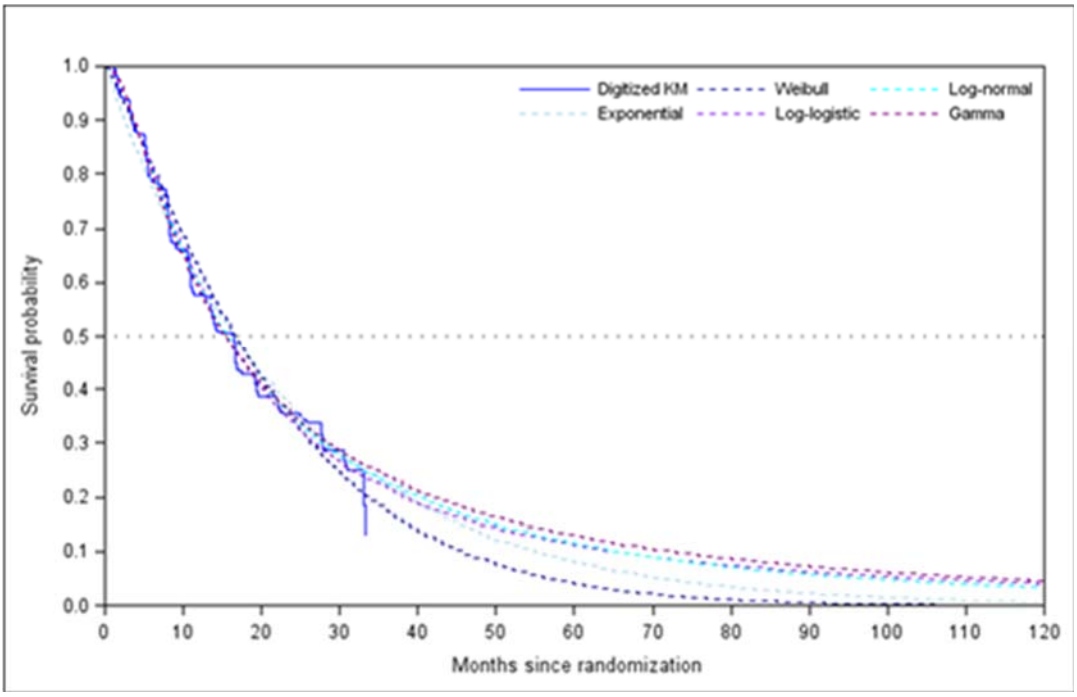


Figure D4 Long term rPFS



10.18 Appendix 18: Net benefit sorting

Figure D5 Tornado diagram with incremental net benefit spread for enzalutamide vs abiraterone

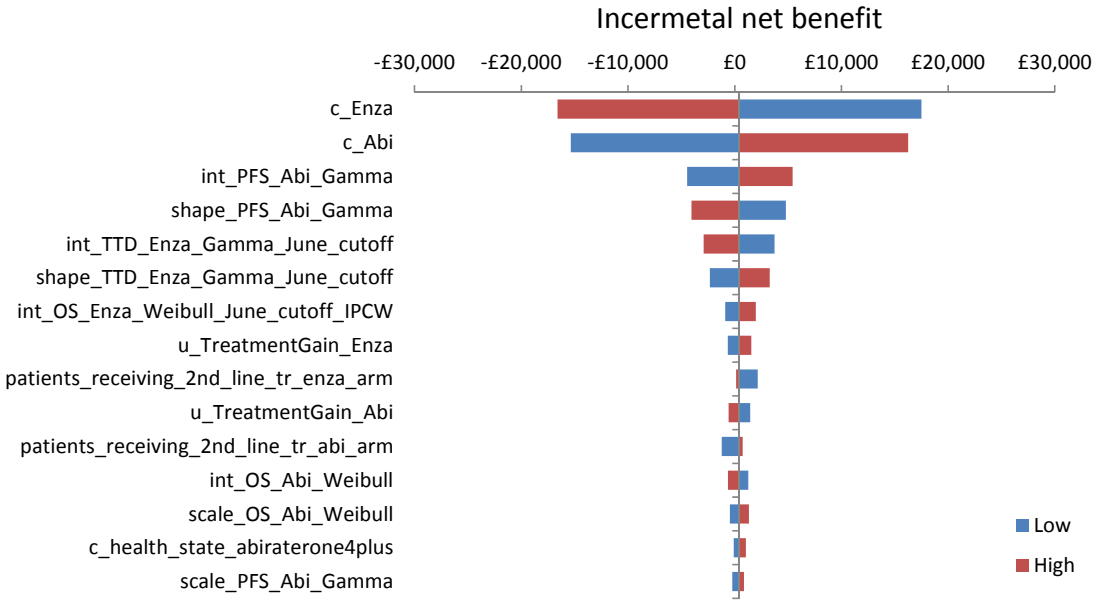
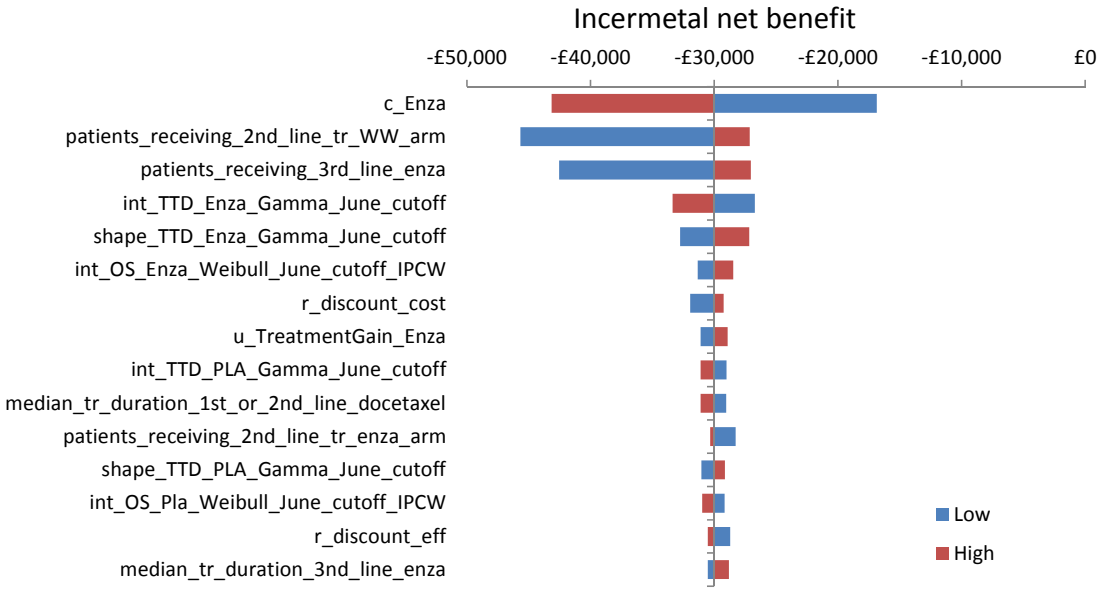


Figure D6 Tornado diagram with incremental net benefit spread for enzalutamide vs BSC



10.19 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.20 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.ukwww.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be

completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for

NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

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