NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Abiraterone Acetate (Zytiga®) for the Treatment of metastatic castration resistant prostate cancer following previous cytotoxic therapy

Contents

List of tables

List of figures

List of abbreviations

AA	Abiraterone acetate
AAP	Abiraterone acetate + prednisone
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike's Information Criterion
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
ASCO GU	American Society of Clinical Oncology Genitourinary Cancers
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUA	American Urological Association
AWMSG	All Wales Medicines Strategy Group
b.i.d.	Bis in die (twice daily)
BFI-SF	Brief Fatigue Inventory-Short Form
BNF	British National Formulary
BP	Blood pressure
BPI-SF	Brief Pain Inventory–Short Form
BSC	Best supportive care
CEA	Cost effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRPC	Castration resistant prostate cancer
CSR	Clinical study report
CT	Computer tomography
CTC	Circulating tumour cells
CUA	Cost utility analysis
DHEA	Dehydroepiandrosterone
DSP	Disease Specific Programme
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EoL	End of life
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
EQ5D	EuroQoL-5 Dimensions

ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FBC	Full blood count
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
HADS	Hospital Anxiety and Depression Score
HR	Hazard ratio
HRQL/HRQoL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost effectiveness
IDMC	Independent Data Monitoring Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone releasing hormone
LHRHa	Luteinising hormone releasing hormone agonist
LYG	Life years gained
MBD	Metastatic bone disease
mCRPC	Metastatic castration resistant prostate cancer
MDT	Multi-disciplinary team
MP	Mitoxantrone + prednisolone
mPFS	Modified progression free survival
MRI	Magnetic Resonance Imaging
MRU	Medical resource utilisation
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OS	Overall survival
PASLU	Patient Access Scheme Liaison Unit
PFS	Progression free survival
PP	Placebo + prednisone
PPI	Present pain intensity
PPSs	Post progression survival
PRO	Patient reported outcomes
PSA	Prostate specific antigen
PSAWG	Protocol-specific prostate cancer working group
PSS	Personal Social Services

P-Y	Patient years
q.d.	Quaque die (once daily)
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria In Solid Tumours
rPFS	Radiographic progression-free survival
SAE	Serious adverse events
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidance Network
SMC	Scottish Medicines Group
SMR	Skeletal morbidity rate

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key

study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Disease Background

- In 2006, NICE estimated that there were 10,448 men with mCRPC in England and Wales; 0.0195% of the population.[1] Using 2011 population estimates,[2] this equates to 10,856 men, which could be expected to increase to 11,238 in 2016. Clinical opinion estimates that 40%[3] of the mCRPC population will receive treatment with docetaxel (4,400 men).

- Localised prostate cancer is caused by genetic mutations that override normal cell proliferation and differentiation controls. Further mutations lead prostate cancer cells to become invasive, spreading to the surrounding tissues, including lymph nodes, distant tissues and organs.[4]

- Metastatic castrate resistant prostate cancer (mCRPC) is diagnosed when tumours spread outside of the prostate, despite treatment to inhibit androgen production in the testes. The five-year survival rate is significantly worse in prostate cancer patients with distant metastases, only 31% compared to almost 100% in those with localised disease.[5]

- The main symptoms of metastatic disease include, weight loss (and loss of appetite), lower extremity pain, oedema and skeletal related events (SREs).[6, 7] Quality of life declines significantly as the disease progresses, patients suffer from fatigue, sexual disturbances, and interruption of social relationships.[8] Once the disease progresses to the metastatic stage, patients complain of general fatigue, cancer pain, restriction of daily life, and urinary disturbance.[9] The most significant morbidity in mCRPC is bone metastasis, and the presence of SREs (pathologic fractures and spinal cord compression) is significantly associated with poorer quality of life.[10]

Abiraterone Acetate

- Abiraterone acetate (Zytiga®), is licensed with prednisone or prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.
- Abiraterone acetate converts to abiraterone, a potent androgen biosynthesis inhibitor, and acts at three sites in the body (testes, adrenal glands and within the prostatic tumour) to delay progression of the disease and improve survival, without compromising patient quality of life.
- Abiraterone acetate is an oral formulation, is taken continuously during the treatment period and should be taken until clinical assessment of disease progression.
- Patients take four (250mg) tablets once daily; 1000mg/day. The list price of abiraterone acetate for one 120 tablet pack is £2,930 (30 days supply). Janssen is also submitting a proposal to the Patient Access Scheme Liaison Unit (PASLU) regarding a patient access scheme for abiraterone acetate. [redacted]
- Abiraterone acetate offers a step change that will alter the treatment pathway for patients with progressing disease following 1st line docetaxel, where currently there are no treatment options to extend survival or delay disease progression that are supported by NICE guidance.

Clinical evidence

- The key evidence presented in the submission is drawn from a large, multi-centre, randomised controlled trial (n=1195) COU-AA-301, comparing abiraterone acetate + prednisolone (AAP) with placebo + prednisolone (PP). This study explored overall survival, progression free survival and quality of life in subjects with mCRPC whose disease had progressed during or after docetaxel-based chemotherapy.
- One interim analysis for the COU-AA-301 study was planned after 67% (534) deaths had occurred and a final analysis was planned after observing 797 total deaths. Upon review of the interim efficacy data, the independent data monitoring committee (IDMC) concluded that the pre-specified efficacy boundary had been met and that there was significant benefit in overall survival (OS) for subjects receiving AAP. The data from the interim analysis (12.8 months follow-up) constituted the 'Primary' Analysis of COU-AA-301 and has recently been published.[11] The 'Primary' Analysis formed the basis of the regulatory submissions and these results led to the recent Marketing Authorisation in Europe via an accelerated assessment procedure. A further follow-up analysis ('Updated') was conducted when 775 deaths had occurred. The results of the 'Primary' and 'Updated' data are presented in this submission, whilst the economic evaluation focuses on the 'Updated' analysis as the data is more mature (20.2 months median follow-up).
- In the study, abiraterone acetate significantly improved median OS by 41% (20.2 months median follow-up). Median survival in the AAP arm was 4.6 months longer than PP at the 'Updated' analysis time point (15.8 (95% CI 14.8, 17.0) vs. 11.2 (95% CI 10.4,13.1)). This treatment effect on OS remains significant after conducting multi-variate analysis to adjust for baseline covariates. The treatment effect also remains for each of the pre-specified subgroups. Overall survival for those patients with 'One Prior Chemotherapy' in the 'Updated' analysis [redacted].
- In the 'Updated' analysis, subjects receiving AAP also had a significantly decreased risk of progression whether measured by radiographic progression ([redacted]) or when treatment discontinuation is used as a proxy for disease progression ([redacted]). An increased proportion of prostate specific antigen (PSA) responders was also observed for AAP in the 'Updated' analysis, [redacted] as was a greater proportion with an objective tumour response [redacted].
- Adverse events (AEs) associated with taking AAP are generally mild or moderate and manageable with basic medical interventions. Of note, the incidence of individual grade 3 or 4 AEs is low, and did not exceed 10% in the abiraterone arm of the study. The incidence of individual grade 3 or 4 AEs of special interest (hypertension, hypokalaemia, fluid retention/oedema, cardiac disorders, and hepatotoxicity) was also low, not exceeding 4% vs. <1% for PP.
- Subjects receiving AAP were more likely to experience better quality of life whilst experiencing improvement in survival compared to PP. They are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens. In addition, men receiving abiraterone are less likely to experience SREs.

- In summary, AAP improved OS, increased time to disease progression, reduced pain and improved functioning compared to PP. Rates of Grade 3/4 AEs were low and most were manageable with basic medical intervention.

The comparators

- The main comparator for abiraterone acetate is best supportive care (BSC), which may include chronic corticosteroids, radiotherapy, oxygen, antibiotics and analgesics used as required. Opinion from clinical advisory panels confirms the comparator arm used in the COU-AA-301 study (placebo + prednisolone + additional supportive care as needed (PP)) was representative of BSC used in the United Kingdom.
- As stated in the scope the submission also compares AAP with mitoxantrone + prednisolone (MP). Clinical opinion suggests that the majority of patients (80%) do not receive 2nd line chemotherapies (mitoxantrone or docetaxel re-challenge) but are treated with BSC.[3] As there is no comparative evidence available to assess the relative efficacy of MP compared to other BSC options in this patient population, the economic evaluation comparing AAP with MP is largely based on assumptions. This comparator is less relevant to the decision problem as it is not commonly used in UK clinical practice in this patient population, but is included in this submission to meet scope requirements.

Economic evaluation

- This submission addresses the cost-effectiveness of abiraterone acetate within its licensed indication compared to the two comparators relevant to the scope PP and MP.
- The base case focuses on the population from the COU-AA-301 study who have only had one prior docetaxel-based chemotherapy regimen; 'One Prior Chemotherapy'. The 'One Prior Chemotherapy' population used in the base case more closely reflects the population that will receive abiraterone acetate in England and Wales. Economic analyses on the ITT population are also presented for completeness.
- A survival based decision analysis model incorporating three health states (progression free survival (PFS), post-progression survival (PPS) and overall survival (OS) was developed in Microsoft Excel. This type of model was chosen as it relies on the observed PFS and OS trial data rather than on an assumed relationship between the PFS surrogate and the final outcome. Men enter the model into the progression free state whereby they receive one of the treatment alternatives (AAP, PP or MP). The probability of death in either progression free or post-progression health states is determined directly from the COU-AA-301 study.
- For this analysis the 'Updated' analysis time point (median 20.2 months follow-up) was used and some further extrapolation was required until all patients had entered the terminal death state.
- Treatment discontinuation from COU-AA-301 has been used as a proxy for PFS in the model as COU-AA-301. Oncologists actively treating prostate cancer 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. Therefore, the clinical decision to stop treatment within the COU-AA-301 study is aligned with how disease progression would likely be determined in UK clinical practice and means treatment discontinuation is an appropriate proxy for PFS in this analysis.
- The base case resulted in an ICER of £52,851 when AAP was compared to the main comparator of interest PP and an ICER of £46,617 when compared to MP, Table 1. Deterministic and probabilistic analyses consistently resulted in ICERs between

£48,451/QALY and £57,298 in PP comparisons and between £42,548/QALY and £50,537/QALY for MP comparisons.

Table 1 Base-case cost-effectiveness results ('One Prior Chemotherapy').

	Abiraterone acetate	Prednisolone	Mitoxantrone
Cost Components (£)			
Drug	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
TOTAL COSTS	[redacted]	[redacted]	[redacted]
Health Outcomes			
LYG	[redacted]	[redacted]	[redacted]
LYG DIFFERENCE	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
QALY DIFFERENCE	[redacted]	[redacted]	[redacted]
ICER	-	£52,851	£46,617
LYG, life years gained; QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios			

Table 2 Incremental cost-effectiveness results ('One Prior Chemotherapy').

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,550	Extended domination by AAP
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£52,851
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Conclusion

- The prognosis of mCRPC patients is poor and those who have progressed after docetaxel currently have a dearth of active treatment options. Patients at this stage of the disease receive BSC, which includes a range of palliative strategies such as corticosteroids or mitoxantrone + prednisolone.
- The economic evaluation showed a base case ICER of £52,851 when AAP was compared to the main comparator of interest PP. The model was robust in sensitivity analysis.
- End of life criteria should be considered when evaluating abiraterone acetate as the prognosis of mCRPC patients is poor[5], the population is small and abiraterone acetate offers a 4.6 month increase in median OS compared to PP.
    - The control arms of the TROPIC[12] and COU-AA-301[13]) studies indicate that after 1st line docetaxel treatment patients have a short life expectancy of approximately one year.
    - Of the 4,400 mCRPC patients estimated to receive docetaxel in the UK, it is estimated that approximately 75% these men would be eligible for treatment with abiraterone (3,300 men). It is estimated that no more than 50% of these men would actually receive treatment with abiraterone acetate.
    - Abiraterone acetate offers this population a 4.6 month increase in median overall survival compared to best supportive care (BSC).[13] The economic model

estimates that the mean OS that could be expected for patients in England and Wales would be [redacted].

- Abiraterone acetate provides this patient group with an important new option which has been shown in a randomised controlled trial to significantly improve quality of life, survival and time to progression compared to supportive care options.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class.

Brand name: Zytiga®

Approved name: Abiraterone acetate

Therapeutic class: The World Health Organisation International Working Group for Drug Statistics Methodology decided to establish a new ATC code for abiraterone in L02BX "Other hormone antagonists and related agents". The new ATC code will be L02BX03 abiraterone acetate.

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

Abiraterone acetate is converted in vivo to abiraterone, a potent androgen biosynthesis inhibitor that selectively inhibits the enzyme 17α-hydroxylase (CYP17). CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, Dehydroepiandrosterone (DHEA) and androstenedione.[14] CYP17 inhibition also results in increased mineralocorticoid production by the adrenals via a feedback loop which culminates in increased adrenocorticotropic hormone (ACTH) secretion. By inhibiting the production of both DHEA and androstenedione, abiraterone acetate blocks androgen biosynthesis at all sites in the body, including the testes, adrenal glands and prostatic tumour. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with luteinizing-hormone-releasing hormone (LHRH) agonists (or orchiectomy).[14]

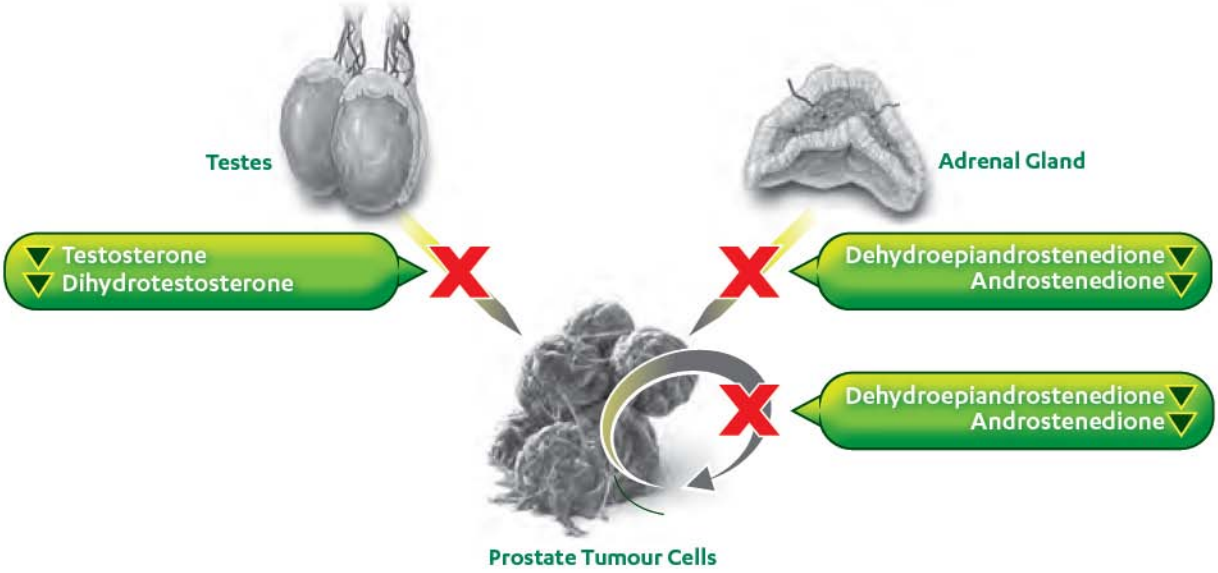


Figure 1. Schematic of the sites where abiraterone acetate blocks androgen biosynthesis, including the testes, adrenal glands and prostate tumour cells.

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

An Accelerated Assessment procedure was agreed-upon by the Committee for Medicinal Products for Human Use (CHMP) on 16th December 2010. CHMP approval was granted 21st July 2011 and the Marketing Authorisation was granted on 7th September 2011.

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 licence).

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus, that the risk-benefit balance of abiraterone acetate in combination with prednisone or prednisolone, in the treatment of mCRPC, in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen, is favourable and therefore recommended the granting of the Marketing Authorisation. Key discussions from the EPAR on abiraterone acetate are as follows.[15]

The EPAR concludes that the overall efficacy results of the study are considered sufficiently mature and clearly positive. The primary endpoint, overall survival (OS), is very relevant to the patient with advanced mCRPC who has received previous chemotherapy with docetaxel and the magnitude of the observed effect (Hazard Ratio (HR) =0.646 'Primary' analysis; HR=0.740 'Updated' analysis) is considered clinically significant. In addition, all the other secondary efficacy endpoints show very consistent results in favour of abiraterone. The safety profile of abiraterone acetate was highly favourable with only a small proportion of treated patients requiring basic medical interventions. Toxicities were generally mild and reversible, and resulted in infrequent dose reductions, dose interruptions, or discontinuations

Key areas of discussion in the clinical review of the EPAR included the impact of administration of abiraterone acetate with medicinal products activated or metabolised by CYP2D6 or that are potent inducers or inhibitors of CYP3A4 on abiraterone acetate pharmacokinetics, exclusion criteria and demographics of patients in COU-AA-301, the incidence of AEs, and the higher incidence of urinary tract infections. The EPAR also discussed the need for liver, kidney and blood pressure monitoring and the potential decrease in bone density associated with abiraterone acetate. Further details on the key areas of discussion in the EPAR are detailed in Appendix 14.

1.5 What are the (anticipated) indication(s) in the UK?

Abiraterone acetate is indicated with prednisone or prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Prednisolone is more commonly used in the UK, and therefore will be referred to throughout the submission.

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 abiraterone acetate that will provide additional comparative evidence in the next 12 months for this indication.

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

Not Applicable.

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

Abiraterone acetate has regulatory approval in the US (FDA approval date granted on 28th April 2011) and Canada (granted 28th July 2011).

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?

Janssen anticipates submitting to the AWMSG in September 2011 with a decision expected early in 2012 and the SMC in November 2011 with a decision expected in May 2012.

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 3 Unit costs of technology being appraised

Pharmaceutical formulation	Abiraterone acetate in combination with prednisolone
Acquisition cost (excluding VAT)	£2930 per 30 days [redacted]
Method of administration	Oral
Doses	1g (four x 250 mg tablets) once daily
Dosing frequency	Daily until disease progression following clinical assessment
Average length of a course of treatment	8 months median treatment duration[11]
Average cost of a course of treatment	Median treatment cost is £23,440 [redacted]
Anticipated average interval between courses of treatments	Abiraterone acetate is administered daily until disease progression (defined by progression of clinical symptoms and/or radiological assessment and/or prostate specific antigen (PSA) progression). There is no evidence that treatment beyond progression is associated with additional benefit.
Anticipated number of repeat courses of treatments	There is no evidence to support repeat treatment with abiraterone acetate after clinical disease progression.
Dose adjustments (as specified in SPC) [14]	No dose adjustment is necessary for patients with pre existing mild hepatic impairment. Abiraterone acetate should not be used in patients with pre existing moderate or severe hepatic impairment. For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required. Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction. However, there is no clinical experience in patients with prostate cancer with severe renal impairment. Caution is advised in these patients.

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?

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. Clinical opinion suggests that monitoring after this initial three month period would be carried out during alternate specialist nurse or oncologist visits.[16] No further monitoring outside of these visits is anticipated.

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

Clinical opinion suggests that this monitoring is similar to the routine monitoring that occurs in this patient population every six weeks.[3]

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?

Abiraterone acetate is indicated for use with prednisolone. The recommended dosage of prednisolone is 10 mg daily.[14]

2 Context

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.

The development of localised prostate cancer is caused by genetic mutations that override normal cell proliferation and differentiation controls.[4] Further mutations enable neoplasms to become invasive, with prostate cancer cells spreading to the surrounding tissues, including lymph nodes, distant tissues and organs.[4] Although androgen deprivation therapy (ADT), to eliminate testosterone production and secretion by the testes, often arrests prostate cancer growth and delays progression,[17] genetic mutations can lead to tumours becoming more sensitive to androgens causing tumour proliferation even when castrate levels of blood testosterone are observed. In addition, prostate cancer cells can also develop the capability to produce its own supply of androgens, which further drives disease progression.[18]

mCRPC is diagnosed when tumours spread outside of the prostate, despite ADT. The 2010 European Association of Urology (EAU) guidelines recommend that diagnosis of mCRPC should be established by measuring serum levels of testosterone, PSA increases and radiographic progression of tumour lesions.[19]

Although prognosis for early stage prostate cancer is good, it is significantly worse for mCRPC. The five-year survival rate is significantly worse in prostate cancer patients with distant metastases, only 31% compared to almost 100% in those with localised disease.[5] The main symptoms of metastatic disease include weight loss (and loss of appetite), lower extremity pain, oedema due to obstruction of venous and lymphatic tributaries by nodal metastases and SREs.[6, 7] Uremic symptoms can also occur from urethral obstruction.[6] During metastatic progression, up to 90% of patients experience metastases to the bone.[7] Bone metastasis can give rise to skeletal related complications such as spinal cord compression, fractures and pain in up to 40% of patients.[7]

In addition to clinical symptoms, prostate cancer, as with other cancers, is associated with a substantial psychological burden on patients; most commonly anxiety and depression. A recent study revealed that 38% of men with prostate cancer reported scores at or above the cut-off for psychological distress (15 or above combined score using the Hospital Anxiety and Depression Score (HADS) instrument).[20] Disease stage is also a significant predictor for poorer mental health in prostate cancer.[21] Mental health is further impacted by

chemotherapy, in particular depression, but also decreased delayed psychological recovery and mood disturbances.[22-26]

Alongside the clinical burden of metastatic disease, prostate cancer has a significant impact on quality of life. The most frequent and severe complaints of patients with mCRPC are related to bone pain, fatigue, sexual disturbances and interruption of social relationships,[8] which contribute to the observed decrease in health related quality of life (HRQL) in patients with metastatic disease.[27]

2.2 How many patients are assumed to be eligible? How is this figure derived?

In 2006, NICE estimated that there were 10,448 men with mCRPC in England and Wales; 0.0195% of the population.[1] Using 2011 population estimates,[2] this equates to 10,856 men and could be expected to increase to 11,238 in 2016.

Clinical opinion estimates that 40%[3] of the mCRPC population will receive treatment with docetaxel (4,400 men). This estimate is aligned with a recent publication, highlighting that the number of men receiving chemotherapy[a] increased from 11% in 2002 to 33% in 2008 within the Thames Valley Cancer Network.[28]

Of the 4,400 men estimated to receive docetaxel, it is estimated that approximately 75% these men would be eligible for treatment with abiraterone acetate (3,300 men), a figure which accounts for those patients that may die on docetaxel treatment, may experience rapid deterioration on docetaxel (not be suitable for further treatment) or those men in whom abiraterone acetate may be contraindicated. This estimate of 75% is based on the number of patients surviving treatment on docetaxel at one year.[29]

2.3 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.

A Technology Appraisal for docetaxel in prostate cancer was published in 2006,[30] and the guidance from this technology appraisal was subsequently incorporated into the Prostate Cancer guidelines on diagnosis and treatment in 2008.[31] Summary recommendations from the Prostate Cancer Guidelines relating to metastatic disease are as follows:

Management of patients with hormone-refractory (castration resistant) prostate cancer should be discussed with the multi-disciplinary team (MDT) with a view to seeking advice from an oncologist and/or specialist in palliative care as appropriate. In these patients treatment with luteinising hormone releasing hormone agonists (LHRHa) is usually continued after withdrawal of anti-androgen treatment. Chemotherapy and/or corticosteroids are recommended for use in this patient population to slow disease

[a]Harris et al., (2011) used the mortality of prostate cancer patients as a proxy for the prevalence of late stage disease, as information on prostate cancer stage in the UK is not currently routinely available.

progression, whilst other therapies target the symptoms of the disease such as bone pain and urinary tract and bowel complications.

- Chemotherapy may be given to men with symptomatic progression or asymptomatic metastatic disease who have rapidly rising PSA. The only chemotherapy regimen licensed for treating this patient population is docetaxel and prednisolone, and this may only be used if their Karnofsky performance status score is 60% or more. Docetaxel treatment should be stopped at the completion of planned treatment of up to 10 cycles or if severe AEs occur, or if disease progression occurs (assessed by clinical or laboratory criteria or imaging studies). Repeat cycles of docetaxel are not recommended if the disease recurs after completion of the planned course of therapy. Men with poor performance status who may not tolerate docetaxel are usually treated with the combination of mitoxantrone and prednisolone. It is not clear whether there is a significant benefit from second line treatment with mitoxantrone or newer chemotherapy drugs for men who have failed docetaxel.
- Corticosteroids can be useful in hormone refractory (castrate refractory) disease to reduce the production of adrenal androgens and higher doses can have an anti-inflammatory effect on bone metastases.
- Bisphosphonates (oral or intravenous route) may be considered for pain relief when other treatments (analgesics and palliative radiotherapy) have failed, but are not recommended to prevent or reduce the complications of bone metastases. In addition, bisphosphonates should not be used to routinely prevent osteoporosis in men receiving androgen withdrawal therapy.
- Strontium-89 should be considered for men with painful bone metastases, especially those unlikely to receive chemotherapy
- Decompression of the upper urinary tract (by nephrostomy or a stent) should be offered to men with obstructive uropathy
- Palliative radiotherapy to the bladder base and prostate may be effective in controlling bleeding causing haematuria
- A defunctioning colostomy may be needed as a result of complete obstruction of the bowel, when narrowing cannot be controlled by diet, aperients or radiotherapy.

Palliative interventions at any stage should be integrated into coordinated care, and any transitions between care settings should be facilitated as smoothly as possible.

NICE has produced other interventional procedure guidelines relating to prostate cancer, as outlined below, however these are primarily focused on treating localised prostate cancer and not mCRPC:

- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. 2006.
- Cryotherapy as a primary treatment for prostate cancer. 2005.
- Low dose rate brachytherapy for localised prostate cancer. 2005.
- Cryotherapy for recurrent prostate cancer. 2005.
- High-intensity focused ultrasound for prostate cancer. 2005.

The EAU has also produced two guidelines on the treatment of prostate cancer, one focused on localised disease[19] and the other on advanced, relapsing and castrate-resistant prostate cancer. [32] To summarise, the EAU guideline recommends LHRH agonists as the standard of care in metastatic prostate cancer.[32] Treatment of mCRPC may include second-line hormonal therapy, novel agents, and chemotherapy with docetaxel at 75 mg/m2 every 3 weeks. Zoledronic acid and denusomab can be used in

men with CRPC and osseous metastases to prevent skeletal-related complications. Following initial docetaxel treatment, one of the potential approaches is docetaxel rechallenge in previously responding patients. In all other situations, vinorelbine, mitoxantrone, or molecular targeted therapy might be considered.

2.4 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.

The current treatment options used to manage metastatic disease as outlined in the current NICE guidelines[31] are presented in Figure 2.

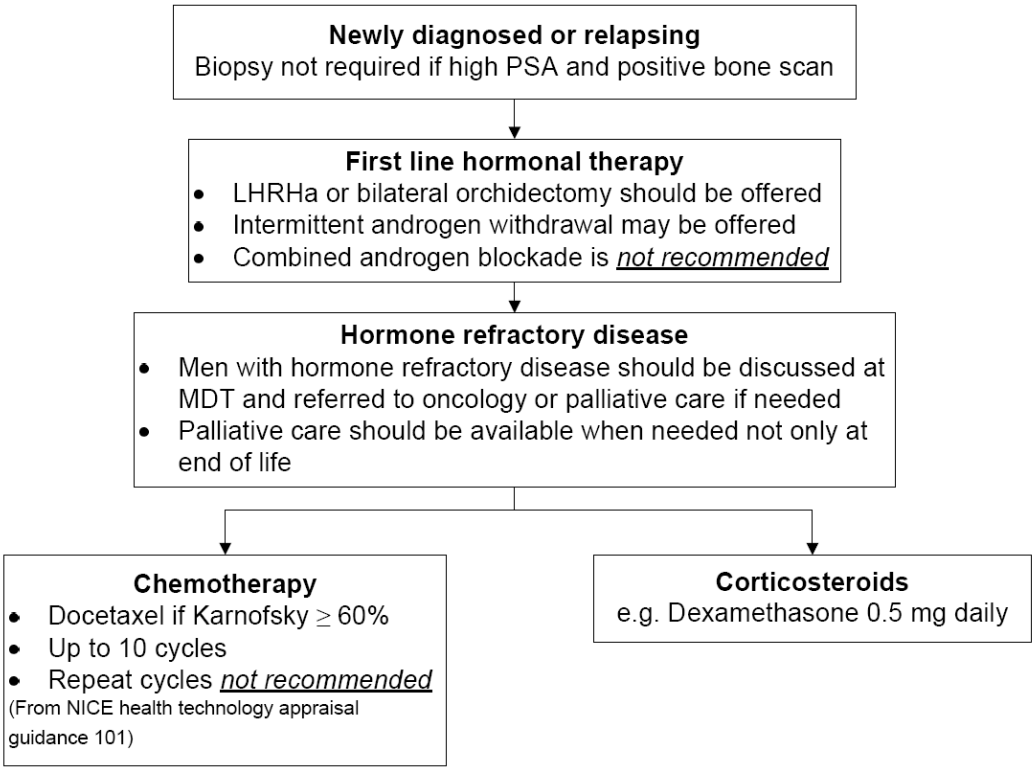


Figure 2 NICE guideline: Prostate cancer algorithm for the treatment of metastatic disease

The only treatments with clinical evidence to slow disease progression and improve OS for mCRPC are chemotherapy (docetaxel) and corticosteroids.[31] Cabazitaxel (licensed 2011) is currently under evaluation by NICE so its place in the clinical care pathway is yet to be determined. Clinical opinion at a recent consensus meeting, which was convened by our Company, suggested that after docetaxel, only a small proportion of patients currently receive a 2nd line chemotherapy (10% mitoxantrone and 10% docetaxel re-challenge) compared to the majority of patients (80%) who will receive BSC (including treatment with prednisolone and other steroids), Figure 3. Schematic of current treatment pathway in mCRPC as determined by expert clinical opinion in the consensus meeting.{GfK Healthcare, 2011 264 /id}.[3] This approach to the treatment of patients with prior docetaxel

use is likely due to the absence of RCT evidence demonstrating OS benefit for either docetaxel retreatment or mitoxantrone in this patient population.

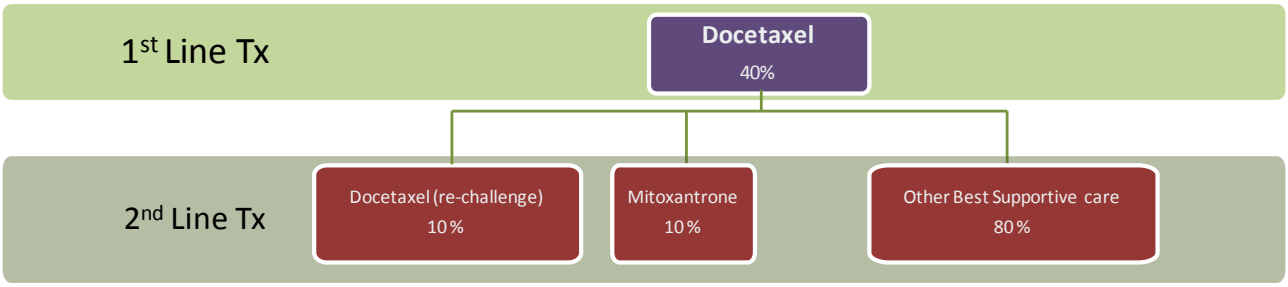


Figure 3. Schematic of current treatment pathway in mCRPC as determined by expert clinical opinion in the consensus meeting.[3]

Abiraterone acetate offers a step change that will alter the treatment pathway for patients with progressing disease post-chemotherapy, where currently there are no treatment options to extend survival or delay disease progression that are supported by NICE guidance. Abiraterone acetate offers a significant survival advantage over BSC, whilst improving or maintaining patient quality of life. Abiraterone acetate is an oral tablet taken daily until disease progression, whereby treatment should then be withdrawn. Abiraterone acetate is administered as a single daily dose of 1g (four 250 mg tablets) with 10 mg prednisolone and, in accordance with the SPC, requires blood monitoring every two weeks in the first three months and then monthly thereafter. In contrast to IV treatments used in clinical practice in the UK in this patient population, oral treatment can be taken at home, without accumulating the medical resource utilisation of healthcare professional time and medical equipment associated with IV administration.

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

Given the historical lack of any licensed, evidence-based treatment options, there is a variability and uncertainty relating to current best practice between localities for patients with mCRPC following treatment with docetaxel. For example, although not recommended by NICE or supported by randomised control trial evidence, clinical opinion suggests that in some regions docetaxel re-challenge is permitted, whilst in others it is not. For patients with progressing disease post-chemotherapy there are currently no recommended treatment options to extend survival or delay disease progression. Hence all clinical decisions in this patient population are focused around the patient's functional status, ability to tolerate further chemotherapy and whether the patient may be expected to have some palliative benefits such as pain relief from chemotherapy.

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

Chemotherapy and corticosteroids are recommended for use in the mCRPC population to slow disease progression, whilst other therapies target the symptoms of the disease such as bone pain and urinary tract and bowel complications.[31] NICE clinical guidelines

(CG58)[31] state that the available treatment options at that time did not demonstrate an OS benefit in the post-chemotherapy population.

The main comparator for abiraterone acetate is therefore BSC (which may include chronic corticosteroids, radiotherapy, oxygen, antibiotics and analgesics used as required). Opinion from clinical advisory panels advocated that the comparator arm used in the COU-AA-301 study (placebo + prednisolone + additional supportive care as needed) is representative of BSC used in the United Kingdom. In addition, clinical opinion concluded that the majority of patients in this patient population (80%) are treated with BSC.[3] In the COU-AA-301 study, the following supportive care options (in addition to chronic steroids) were permissible in both treatment arms:[33]

- LHRH agonists to maintain testosterone <50ng/dL
- Conventional multivitamins, selenium and soy supplements
- Additional acute systemic glucocorticoid administration used as a “stress dose”
- Bisphosphonate if patients were on the medication prior to study baseline
- Transfusions and hematopoietic growth factors.

Therefore the prednisolone arm used in the COU-301-AA (representative of supportive care) should be considered the most appropriate comparator for abiraterone acetate in this patient population in alignment with the decision problem.

The other comparator stated in the decision problem is mitoxantrone + prednisolone (MP). Although NICE clinical guidelines (CG58)[31] state that MP may be considered as a first line treatment option for men with poor performance status who may not tolerate docetaxel, these NICE guidelines also state that it is not clear whether there is a significant benefit from second line treatment with MP for men who have failed docetaxel.[31] Given the lack of survival advantage demonstrated in first line therapy and the potential for severe life-threatening complications, it is understandable that its place in this more difficult to treat second line population is debated, even as a palliative treatment. Clinical opinion concurs; whilst the majority of men are unlikely to undergo 2nd line chemotherapy, only a small proportion (10%) receive MP following their 1st line docetaxel treatment.[3] Due to the lack of RCT evidence comparing MP with BSC in this patient population coupled with the low use of MP post-docetaxel in the UK, MP is not considered to be a relevant comparator for abiraterone acetate, but is included as a comparator to comply with the scope.

Cabazitaxel is not an appropriate comparator for abiraterone acetate in this submission, as it is currently under evaluation by NICE and discussions at the scoping meeting concluded that cabazitaxel and abiraterone should be considered as separate STAs. It was also noted by clinical experts at the abiraterone acetate Scoping Workshop that although both agents are intended for use in broadly similar populations, abiraterone acetate would likely be used to defer the use of cabazitaxel until a later stage.

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

In a small number of cases, abiraterone acetate may cause hypertension, hypokalaemia and fluid retention,[14] however co-administration of a prednisolone results in a reduction in these AEs. In these cases, anti-hypertensive agents would be administered to those with hypertension, potassium supplements and/or aldosterone antagonists given to those with hypokalaemia and diuretics for those with oedema.[15]

2.8 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 abiraterone acetate is administered orally and in the patient's home, there are no anticipated costs due to location of care, staff and administration. Abiraterone acetate requires two-weekly monitoring during the first three months of treatment[14] and this monitoring would be carried out as an outpatient visit to an oncologist clinic.[3] After, this initial monitoring period, the frequency of follow-up visits would be similar to that of other treatment options in this patient population.[3]

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

As abiraterone acetate is an oral tablet that can be taken in the patient's home, it is not anticipated that additional infrastructure will be required. As outlined above, during the first three months of treatment with abiraterone acetate, fortnightly monitoring of liver function is required. This monitoring is common for all drugs administered in this post-chemotherapy population and therefore additional infrastructure is not anticipated.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

The Company are not aware of any issues relating to equity or equalities in NICE guidance or protocols for the treatment of mCRPC.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Men with metastatic, castrate-resistant prostate cancer whose disease has progressed on or after docetaxel-based chemotherapy	The submission will address the clinical and cost-effectiveness of abiraterone acetate within its licensed indication. The base case focuses on the patients who have only received one prior docetaxel-based chemotherapy regimen; 'One Prior Chemotherapy'. The 'One Prior Chemotherapy' population used in the base case more closely reflects the population that will receive abiraterone acetate in England and Wales. Clinical and economic analyses on the ITT population are also presented for completeness.	N/A
Intervention	Abiraterone acetate in combination with prednisolone	Abiraterone acetate (1g q.d) in combination with 10mg prednisolone (5mg b.i.d)	N/A
Comparator(s)	• Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies and corticosteroids) • Mitoxantrone alone or in combination with prednisolone	• BSC, represented by the prednisolone (10mg) arm of the COU-AA-301 study which included supportive care (radiotherapy, bisphosphonates, LHRH agonists as needed). Expert clinical opinion suggests that the prednisolone arm of the COU-AA-301 study is reflective of best supportive care in the UK. • Mitoxantrone (12 mg/m^2 every 3 weeks) in combination with prednisolone (10mg). A systematic review of the literature determined that with respect to OS that there is no published evidence to suggest that MP offered increased survival; this is supported by UK clinical opinion. Therefore, in the absence of comparative clinical evidence in this patient population, the OS from the prednisolone arm of the COU-AA-301 study is assumed to be the same for the MP comparison.	N/A
Outcomes	• Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life.	In this submission a range of outcome measures will be used to compare the clinical effectiveness of abiraterone acetate to the BSC comparator as assessed within the COU-AA-301 study. These are as follows: • OS (primary endpoint) • Progression-free survival (PFS): 1) radiographic PFS (rPFS) (secondary endpoint) 2) modified PFS 3) time to treatment discontinuation • Response rate: 1) Objective tumour response 2) PSA response: the number of patients achieving a decrease of PSA by at least 50% 3) Circulating tumour cells (CTC) response: the proportion of patients achieving circulating tumour cell conversion • PSA response defined as the average PSA response (secondary endpoint) • Adverse effects of treatment • Health-related quality of life was assessed using the validated and disease specific Functional Assessment of Cancer Therapy - Prostate (FACT-P) questionnaire. The Brief Pain Inventory–Short Form (BPI-SF) and the Brief Fatigue Inventory-Short Form (BFI-SF) were assessed	N/A

		monthly until treatment discontinuation. Specific FACT-P was assessed prior to treatment on Day 1, every 12 weeks for the first 9 months then half yearly thereafter until discontinuation. Quality Adjusted-Life Years (QALYs) are an output from the economic analysis and were derived through mapping FACT-P to EQ5D using an algorithm determined from the results of the Adelphi Disease Specific Program in Prostate Cancer, which captures both FACT-P and EQ5D. For comparisons with MP, due to the lack of comparative RCT or non-RCT evidence comparing prednisolone with MP several assumptions are necessary when modelling these outcomes in the absence of robust clinical data.	
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.	To inform the analysis, the base case model uses data from the 'Updated Analysis' of the COU AA 301 study for the 'One Prior Chemotherapy' population (70% of ITT).The population in the base case analysis more closely reflects the UK population which has lower use of chemotherapies after 1st line docetaxel than in the COU-301-AA study, and is therefore reflective of the population who would be eligible to receive abiraterone acetate in the UK, see Section 5.5.1 and 6.2 for more detail. The cost-effectiveness model is a survival based decision analysis model that compares abiraterone acetate with PP and MP. The incremental cost per QALY has been generated using OS measured directly from the 301 trial and the mapping algorithm outlined above. A time horizon of ten years has been applied as the majority of patients at this stage of disease are not alive at 7 years. This time horizon is in alignment with models for other late stage cancers. Costs are considered from an NHS and Personal Social Services perspective	N/A
Subgroups to be considered	If evidence allows, consideration will be given to subgroups defined by • baseline Eastern Cooperative Oncology Group (ECOG) status • extent of prior taxane exposure • time since taxane treatment	Analyses of the effect of abiraterone acetate on OS were consistent across all pre-specified patient subgroups in the 'Primary' analysis. Subgroup analyses determined that those with only one prior line of chemotherapy 'One Prior Chemotherapy' or ECOG 0-1 have a lower risk of death, however the relative benefit of AAP is not statistically significantly different between 'One Prior Chemotherapy' subgroup vs. >1 prior chemotherapy, nor between ECOG 0-1 vs. ECOG >1. Time since prior taxane treatment was not a pre-specified stratification factor and therefore this subgroup was not explored. The 'One Prior Chemotherapy' population (70% of ITT) is used in the base case of the economic analysis as this population is more likely reflective of the UK population that will receive abiraterone acetate as per the licence.	N/A
Special considerations, including issues related to equity or equality	None	End of life criteria should be considered for abiraterone acetate for this indication; Men with mCRPC whose disease has progressed on or after docetaxel-based chemotherapy - mCRPC patients have a median overall survival of about one year[12, 13] - A maximum of 3,300 patients is assumed to be eligible for abiraterone acetate (Section 2.2) - 4.6 month increase in median overall survival compared to BSC	N/A

Section B – Clinical and cost effectiveness

5 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.

5.1 Identification of studies

5.1.1 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 9.2, appendix 2.

A full systematic review has been conducted to identify all abiraterone acetate studies, as well as all potential comparator trials, conducted in mCRPC patients, with the aim of restricting the trials to those conducted in post-chemotherapy populations to align with the decision problem. Alongside the interventions outlined in the decision problem, all other trials involving common interventions used for the treatment of mCRPC were included. The network of evidence identified during this review is presented in Table 19 and Figure 13.

Databases were searched up until 30th May 2011 with no restriction on the start date. The conference proceedings were searched from 2006 and were inclusive of the ASCO conference (resulting in a cut-off date of 8th June 2011). A comprehensive literature search of four electronic databases has been conducted:

- MEDLINE
- MEDLINE In-process
- Excerpta Medica Database (EMBASE)
- Cochrane Central Register of Controlled Trials (CENTRAL).

The following conference proceedings were searched:

- American Society of Clinical Oncology (ASCO) Annual meeting (2006 - 2011)
- American Society of Clinical Oncology Genitourinary Cancers symposium (ASCO GU) (2006 - 2011)
- American Urological Association (AUA) (2006 - 2011)
- European Association of Urology (EAU) (2006 - 2011)
- European Society for Medical Oncology (ESMO) (2006 - 2010).

To be included in the review, trials had to meet pre-defined eligibility criteria pre-specified in the systematic review protocol; studies were to have a full-text English publication to be included (full inclusion criteria, listed in Section 5.2). Abstracts of citations found through the searches were initially reviewed for inclusion, based on the title and abstract alone. Full-text copies of the studies, which potentially met the inclusion criteria, were obtained. In instances where it was not possible to determine whether some studies met the inclusion criteria based on their abstracts alone, the full texts were obtained for further assessment. Following receipt of all the full-text papers, the inclusion criteria were applied to full-text

trials, which were included or excluded accordingly. To avoid falsely excluding any studies in the post-chemotherapy mCRPC population (the population relevant to the decision problem), studies were not classified as pre-chemotherapy, post-chemotherapy or mixed populations (i.e. included pre- and post-chemotherapy) until the full-publication had been reviewed. Studies that met the eligibility criteria after the second screening stage were included in the qualitative synthesis.

Data from the studies was extracted by two independent analysts and any discrepancies identified were reconciled by a third analyst. A qualitative assessment was conducted on each of the included studies, using the assessment criteria recommended in the NICE manufacturer's template.

5.2 Study selection

5.2.1 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.

Table 4. Table of inclusion and exclusion criteria used in the systematic review

	Clinical effectiveness	Rationale
Inclusion criteria	**Population** Age: Adults (≥18 years) Gender: Any Race: Any Stage of disease: mCRPC	• The patient population has been restricted to match the mCRPC population stated in the decision problem • Since prostate cancer is a disease of adults only, studies including children or adolescents were excluded
	Interventions **Standard of care:** Docetaxel, mitoxantrone, estramustine, cyclophosphamide, 5-fluorouracil, doxorubicin, carboplatin, etoposide, paclitaxel, vinorelbine, vinblastine dexamethasone, hydrocortisone, prednisone/prednisolone,strontium, zoledronate **Investigational interventions:** Abiraterone, sipuleucel T, MDV3100, bevacizumab, atrasentan, dasatinib, ZD4054, patupilone, AS1404, ipilumumab, sunitinib, IMC-A12, aflibercept, cabazitaxel (XRP6258), JM216	• The list covers common interventions used for the treatment of mCRPC
	Comparator Any of the listed interventions, any chemotherapy, best supportive care (includes palliative radiotherapy, corticosteroids, oxygen, analgesics), or placebo	• A wide range of chemotherapy-based combinations are being investigated besides the BSC. These comparators were selected to potentially enable the inclusion of all relevant citations • The exclusion reason of comparator was applicable only for RCTs as these RCTs are the gold standard of clinical evidence • Observational studies and non RCTs were included regardless of the comparator treatment evaluated
	Study design RCTs Non-randomised controlled clinical trials Single-arm interventional studies/uncontrolled trials Observational studies, including: Cohort studies (prospective or retrospective) Case-control studies Cross sectional study/survey	• The review included RCTs, as they are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions • Observational studies were also included in the review as they include a wider patient population and present real life effectiveness data

	Clinical effectiveness	Rationale
	Hospital records and database studies	
	Language restrictions English only	• The restriction would not limit results substantially due to data availability in English language
	Publication timeframe All publications up to and including 30th May 2011 All conference proceedings from 1st Jan 2006 until 8th June 2011	• Studies which are presented at conferences are usually published in journals within 6 years
	Outcome of interest Studies should report at least one of the following outcomes of interest **Outcomes of interest are:** OS PFS Time to progression [according to PSA and (Response Evaluation Criteria In Solid Tumours RECIST) criteria] Response rate (according to PSA and RECIST criteria) Duration of response PSA measurements EORTC QoL questionnaire (EORTC-QLQC30) EuroQol-5D (EQ-5D) Functional Assessment of Cancer Therapy-Prostate (FACT-P) score and its subscale BPI Present pain intensity (PPI) Bone pain Pain response Time to pain progression Time to opiate use Visual Analogue Scale (VAS) pain score Analgesic score Time to first SRE Skeletal morbidity rate (SMR) Vertebral fractures Non-vertebral fractures Adverse Events	• Studies which do not report outcomes of interest were excluded • These outcomes were chosen since these are frequently measured and reported in the trials involving advanced prostate cancer patients
Exclusion criteria	**Population** Disease: Prostate cancer other than mCRPC **No subgroup analysis** No subgroup analysis for disease of interest Or for metastatic disease **Study design** Case studies Case series Case reports **Phase I** **Dose-ranging studies**	• Studies reporting no subgroup data for population of interest (mCRPC) were excluded. However, studies including mixed patient population with the proportion of mCRPC patients being ≥90% were included in the review. • Case-series and case-reports were not included in the review as they are generally smaller, non-comparative studies which are at a higher risk of bias • Phase I studies and dose ranging studies were excluded as they aim to establish the safety profile rather than clinical effectiveness. The results (if presented) would not be interpreted due to the different doses received by patients

5.2.2 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 (www.consort-statement.org/?o=1065).

The systematic review identified five abiraterone acetate studies (one RCT (COU-AA-301)[13] and three single arm studies[34-37]) in the mCRPC post-chemotherapy population.

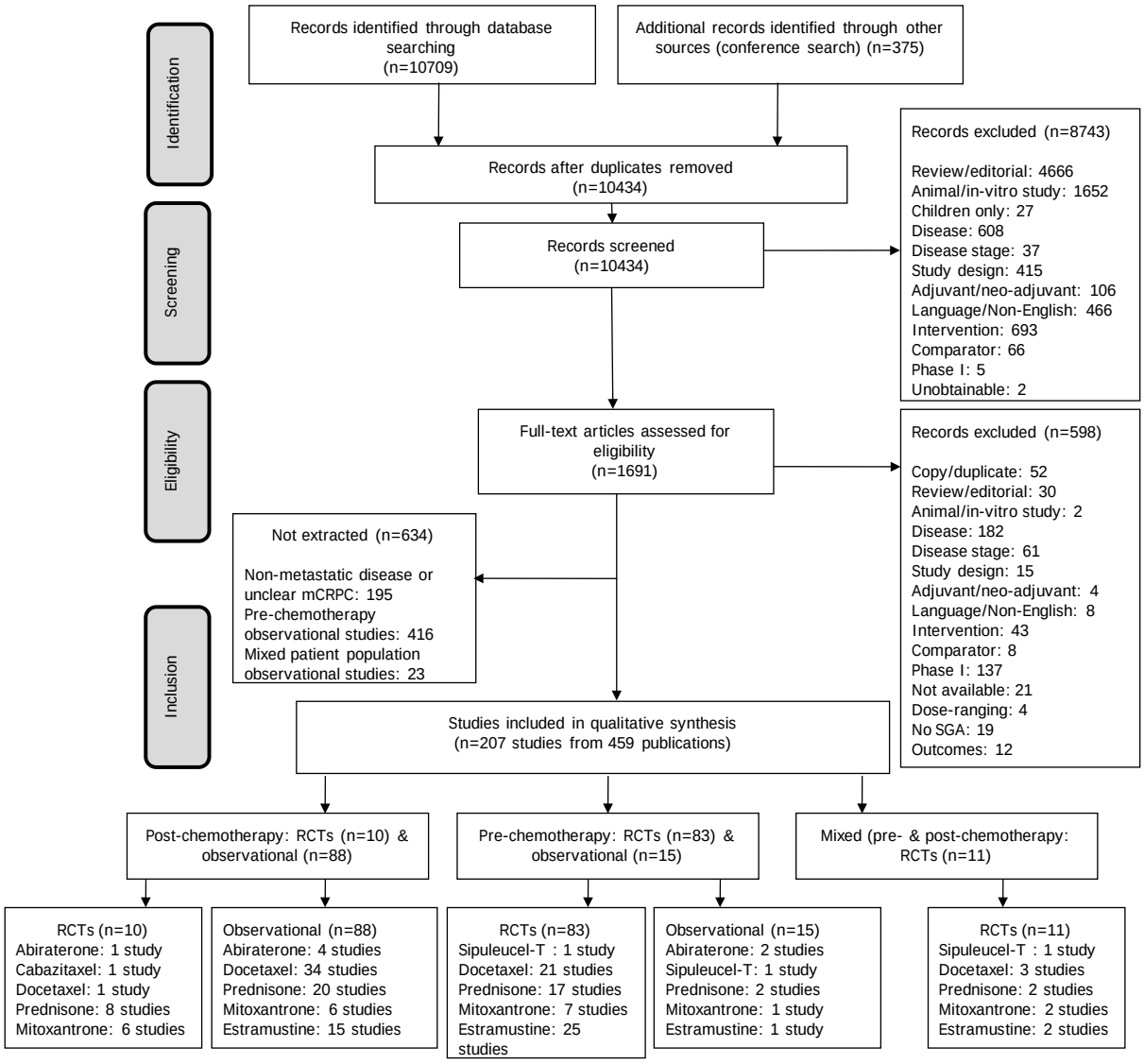


Figure 4. Consort flow of systematic review to identify abiraterone and comparator clinical trials and non-RCT studies.

5.2.3 Please highlight 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)

Data from the primary COU-AA-301 study comparing AAP with PP detailed in this submission is sourced from both published and unpublished sources, listed below. The main publication of the 'Primary' analysis (de Bono et al., (2011)) is supplemented by data in the 'Primary' analysis clinical study report (CSR) and an analysis of the patient reported outcomes (PRO) data. Data from the 'Updated' analysis has been taken from the

Statistical Report and is supplemented by additional analyses presented at ASCO in 2011 [redacted]

- COU-AA-301 'Primary' analysis (12.8 months follow-up) which formed the basis of the regulatory file to the European Medicines Agency (EMA)
    - Publication De Bono, Logothetis et al., (2011)[13]
    - CSR COU-AA-301[38] (unpublished)
    - Analysis of PRO data[39-41]
- COU-AA-301 'Updated' analysis 1 (20.2 months follow-up)
    - Statistical Report of 'Updated' data from Study COU-AA-301[42] (unpublished)
    - Oral presentation at ASCO 2011[43] [redacted]

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group.

Table 5 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study references
COU-AAA-301 (NCT00638690)	Abiraterone acetate (1g q.d) + prednisolone (5mg b.i.d) until disease progression (AAP)	Placebo + prednisolone (5mg b.i.d) until disease progression (PP)	mCRPC patients whose disease has progressed during or after docetaxel-based chemotherapy	COU-AA-301 manuscript[13] Clinical Study Report COU-AA-301[38] Statistical Report of updated analysis of COU-AA-301[42] Analysis of patient reported outcomes data from COU-AA-301[44]

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem.

COU-AA-301 is a Phase III study that compares once daily AAP with PP in patients with mCRPC whose disease has progressed during or after docetaxel-based chemotherapy. This study permits the comparison of AAP with the comparator of primary interest PP, which is representative of BSC in the UK.

In prospective Phase III clinical trials, prednisolone has demonstrated palliative benefits in mCRPC populations.[45, 46] Significant improvements in pain, qualify of life and fatigue were also reported. Guidelines also support the use of corticosteroids, such as prednisolone, for palliative reasons. According to EAU guidelines, many patients with mCRPC have painful bone metastases and are not amenable to chemotherapy,[32] making palliative treatment options, such as corticosteroids, the most appropriate. NICE guidelines also recommend the use of corticosteroids in this patient population.[31]Therefore, the PP arm of the COU-AA-301 study is considered to representative of BSC in the UK and provides evidence directly relating to the intervention and main comparator as outlined in the decision problem.

5.2.6 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.

No other head to head RCTs involving abiraterone were identified and therefore no RCTs have been excluded.

List of relevant non-RCTs

5.2.7 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 5.8 and key details should be presented in a table.

Table 6 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
COU-AA-004 (NCT00485303) Single arm study	Abiraterone acetate (1g q.d) + Prednisone (5mg b.i.d)	mCRPC patients who experienced treatment failure with docetaxel	Single arm Phase II study to evaluate the efficacy and safety of AA in combination with prednisone to reduce the symptoms of secondary hyperaldosteronism in (n= 58)	Danila, Morris et al., (2009)[34]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 36% of patients
COU-AA-003 (NCT00474383) Single arm study	Abiraterone acetate (1g q.d)	CRPC patients with progressive disease and PSA >5ng/mL	Single arm Phase II study to evaluate the proportion of patients achieving a PSA decline of ≥50% (n=47)	Reid, Attard et al., (2010)[37]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 51% of patients
COU-AA-BMA (NCT00544440) Single arm study	Abiraterone acetate (1g q.d) + Prednisone	CRPC with baseline serum testosterone <50ng/dl (82% had prior chemotherapy)	To explore associations between serum (endocrine) and microenvironment (paracrine) androgen concentration and response to abiraterone acetate (n=17)	Logothetis, Wen et al.,(2008)[36]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 41% of patients
		Progressive CRPC patients (61% with 2 or more chemotherapies)	Single arm study to explore the predictive benefit of an "intracrine androgen signalling signature " in patients treated with abiraterone acetate plus prednisone (n=56).	Efstathiou, Tu et al., (2010)[35] (ASCO) presentation	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 46% of patients

5.3 Summary of methodology of relevant RCTs

5.3.1 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 from the single RCT identified by the systematic review, COU-AA-301, has been published in a manuscript[13] and some of the 'Updated' analysis presented at ASCO in 2011.[43] This publicly available data is supplemented by unpublished reports ([redacted]). Whilst most of the methodology of this study is in the public domain, additional detail has been added from these unpublished sources.

Methods

5.3.2 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.

Table 7 summarises the methodology from COU-AA-301.

Table 7 Summary of methodology of the COU-AA-301

Trial no. (acronym)	**COU-AA-301**[38]
Location	United Kingdom (12 UK sites), Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, US (130 sites total)
Design	Phase III, Randomised, Double-Blind study comparing abiraterone acetate + prednisolone vs. prednisolone alone
Duration of study	Patients treated until disease progression
Method of randomisation	Eligible subjects were randomised (2:1) using a centralised Interactive Web Response System (IWRS) and were stratified by baseline ECOG performance status score (0-1 or 2), presence or absence of pain, 1 versus 2 prior chemotherapy regimens, and documented type of prostate cancer progression at entry [PSA progression only versus radiographic progression in bone or soft tissue with or without PSA progression]).
Method of blinding (care provider, patient and outcome assessor)	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 =)	- Abiraterone Acetate + prednisone/prednisolone (AAP) (n=797) - Placebo + prednisone/prednisolone (PP) (n=398)
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint, OS was measured from the date of randomization to the date of death (regardless of cause). Survival time of living subjects was censored at the last date a subject was known to be alive or lost to follow up. The OS distribution and median OS was estimated using the Kaplan-Meier data and hazard ratios from a stratified cox proportional hazards analysis. OS was assessed by telephone interview or chart review three monthly during the study and in follow-up period.
Secondary outcomes	- Time to PSA progression (PSA assessed every three months) - PSA response rate (50% decrease) - rPFS assessed every 3 months
Other endpoints	- Modified PFS - Objective tumour response rate according to modified RECIST criteria - Pain palliation measured by BPI-SF assessed monthly until 9months and at treatment discontinuation - Time to pain progression - Fatigue palliation and time to fatigue progression measured by BFI-SF assessed monthly until 9 months and at treatment discontinuation - Functional status measured by FACT-P assessed every three months for first 9 months and 6 monthly thereafter - Time to first SRE assessed monthly for first 9 months and 3 monthly thereafter - CTC response: in a subgroup of patients for research purposes. CTC enumeration <5 or ≥5 assessed monthly for first 3 months then at treatment discontinuation - AEs and clinical laboratory tests to evaluate safety assessed monthly until 9 months and 3 monthly thereafter, with the exception of fasting glucose, serum lipids, serum testosterone and other androgens and urinalysis which were only measured at screening and discontinuation. - Medical resource utilisation (MRU) information
Duration of follow-up	Up to 60 months

Participants

5.3.3 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.

Table 8 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
COU-AA-301[38]	- Willing and able to provide written informed consent - Men at least 18 years of age - Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology - At least 1 but not more than 2 cytotoxic chemotherapy regimens for mCRPC. At least 1 regimen must have contained docetaxel. If docetaxel-containing chemotherapy was used more than once, this was considered as one regimen. - Documented prostate cancer progression as assessed by the investigator - Ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM) - ECOG performance status score of 2 or less - Adequate bone marrow, hepatic and renal function: Haemoglobin ≥9.0 g/dL independent of transfusion; Platelet count ≥100,000/μL; Serum albumin ≥3.0 g/dL; Serum creatinine <1.5 x upper limit of normal (ULN) or a calculated creatinine clearance ≥60 mL/min - Serum potassium ≥3.5 mmol/L - Able to swallow the study medication as a whole tablet	- Serious or uncontrolled coexistent non-malignant disease, including active and uncontrolled infection - Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg). - Active or symptomatic viral hepatitis or chronic liver disease - Abnormal liver transaminase test concentrations - History of pituitary or adrenal dysfunction - Clinically significant heart disease - Other malignancy, except non-melanoma skin cancer - Known brain metastasis - History of gastrointestinal disorders (medical disorders or extensive surgery) that could have interfered with the absorption of the study medication - Prior therapy with abiraterone acetate or other CYP17 inhibitor(s), or investigational agent(s) targeting the AR for metastatic prostate cancer - Prior therapy with ketoconazole for prostate cancer - Surgery or local prostatic intervention within 30 days of the first dose. - Radiotherapy, chemotherapy, or immunotherapy within 30 days - Any acute toxicities due to prior chemotherapy or radiotherapy that had not resolved - Current enrolment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1 - Condition or situation which, in the investigator's opinion, might put the subject at significant risk, confound the study results, or interfere significantly with subject's participation in the study - Not willing to comply with the procedural requirements of this protocol - Subjects who had partners of childbearing potential who were not willing to use a method of birth control with adequate barrier protection
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		

5.3.4 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.

A summary of the demographics and baseline disease characteristics shows that they were well balanced between the two groups, Table 9. In both groups, 93% of the subjects in both groups were white, the median age was 69 years and 28% of subjects in both groups were 75 years or older. Seventy percent (70%) of subjects in the AAP group, had only ‘One Prior Chemotherapy’, compared to 69% in PP group.

Ten percent (10%) of subjects in the AAP group and 11% of subjects in the PP group had a baseline ECOG performance status score of 2. Most subjects (69.6%) had radiographic progression with or without PSA progression. Forty-five percent (45%) of subjects in both groups had pain at baseline. Eighty-nine percent (89%) of subjects in the AAP group and 90% of subjects in the PP group had bone metastasis.

Table 9 Characteristics of participants in the RCTs across randomised groups (ITT)

COU-AA-301 Baseline characteristic	(AAP)	(PP)
Trial 1 (n = 1195)	**(n = 797)**	**(n = 398)**
Age: mean (SD)	69.1 (8.40)	68.9 (8.61)
Gender: male %	100	100
Race: %		
White	93.3	92.7
Black	3.5	3.8
Asian	1.4	2.3
American Indian/Alaskan	0.4	0.0
Other	1.4	1.3
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Time since initial diagnosis (days): mean (SD)	2610.9 (1630.21)	2510 (1712.36)
PSA at initial diagnosis (ng/ml): mean (SD)	207.60 (835.658)	255.72 (855.441)
TNM stage at initial diagnosis: %		
Stage I	0	0
Stage II	12.9	13.1
Stage III	14.1	12.3
Stage IV	37.3	40.2
Incomplete reporting	35.8	34.4
Gleeson score at initial diagnosis: %		
<7	14.9	10.6
3+4=7	20.1	17.4
4+3=7	13.9	18.0
≥8	51.1	54.0
Evidence of disease progression: %		
PSA only	29.9	31.4
Radiographic progression +/- PSA progression	70.1	68.6
Extent of disease: %		
Bone	89.2	90.4
Node	45.4	41.5
Liver	11.3	7.6
Lungs	13.0	11.4
Prostate mass	7.5	5.8
Other viscera	5.8	5.3
Other tissue	5.0	5.1
Prior cytotoxic therapy		
'One Prior Chemotherapy'	70.0	69.1
>1 type prior chemotherapy	30.0	30.3
ECOG performance status: %		
0 or 1	89.7	88.7
2	10.3	11.3
Pain present: %	44.8	45.0
Baseline PSA (ng/ml): mean (SD)	439.18 (888.476)	400.58 (810.549)
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		

Outcomes

5.3.5 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, 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.

Table 10 Primary and secondary outcomes for COU-AA-301

COU-AA-301	Outcome(s) and measures	Reliability/validity/ current use in clinical practice
Primary outcome	OS: the time from randomisation to death from any cause	OS a patient-relevant outcome and is the key outcome currently used to establish regulatory approval for new treatments.
Secondary outcomes	- Time-to-PSA progression based on protocol-specific prostate cancer working group (PSAWG) criteria - PSA response rate: Proportion of patients achieving a PSA decline ≥ 50% confirmed by a second PSA decline at least 4 weeks later - rPFS based on imaging assessments of soft tissue (according to modified RECIST criteria[b])	Both PSA and disease progression assessed by imaging studies are frequently used in UK clinical practice to assess disease progression Although PFS is not routinely calculated for use in clinical practice, it is a common, but often differentially defined, endpoint used in clinical trials of oncology products. The RECIST criteria is widely used in UK clinical practice.
Other outcomes	- Modified PFS based on meeting one of the criteria for discontinuation of study treatment which involved time to death or first observation of any one of the following (PSA progression, radiographic progression, increase in glucocorticoid use, pain progression, a SRE, or the initiation of a new systemic anticancer therapy - Objective tumour response: Proportion of patients with by modified RECIST criteria - Pain palliation[c]: Proportion of patients experiencing pain palliation using BPI-SF and analgesic score - Time to pain progression[d] - Fatigue progression[e] and time to fatigue progression assessed using the BFI-SF - QOL total score and each subscale score as assessed by FACT-P - Time to first SRE: defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. - CTC response rate: A subject is a responder if the subject's baseline CTC was ≥5 followed by a post-baseline CTC <5 at any visit - AEs and serious adverse events (SAEs) - MRU information	QOL and patient reported outcomes assessments are not routinely conducted in clinical practice in the UK, however these measures are becoming increasingly important for treatment decisions in the UK Bone metastases, present in a large majority of mCRPC patients, develop initially in the axial skeleton and later in the appendicular skeleton. These lesions cause pain, skeletal fractures, spinal cord compression and are the major cause of morbidity in metastatic disease. Skeletal related AEs are therefore central to patient quality of life and are noted to aid the clinical decision making process to assess the benefits of treatment and disease progression and are therefore relevant to the decision problem. CTC assessment is not currently used in routine clinical practice in the UK to assess disease progress The 301 study represents the first randomised controlled trial to evaluate CTCs as a potential surrogate biomarker for survival in metastatic prostate cancer. The aim of including CTCs in the study was to start the process of developing and validating a biomarker or biomarker panel which could be used in the future to accelerate the drug development process in prostate cancer.

[b] Modified RECIST criteria: Baseline lymph nodes≥ 2 cm to be considered as target lesions) or by bone scan (≥ 2 new lesions confirmed ≥ 6 weeks later shows ≥ 1 additional new lesion).
[c] Pain palliation. A subject is a responder if the subject experienced a reduction of ≥30% in the BPI-SF worst pain intensity score over the last 24 hours observed at 2 consecutive evaluations 4 weeks apart without any increase in analgesic usage score (ie, best response). Note: Only subjects whose pain score was ≥4 at baseline were to be analyzed for pain palliation.
[d] Pain progression: BPI-SF increase by ≥30% and an absolute score of ≥4 in the BPI-SF worst pain intensity score over the last 24 hours observed at 2 consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score ≥30% observed at 2 consecutive evaluations 4 weeks apart with a BPI-SF score of ≥4
[e] Fatigue progression: Responders had two consecutive follow-up visits where the score on BFI Item #3 (Worst fatigue in last 24 hours) had increased by at least 2 points since baseline.

Statistical analysis and definition of study groups

5.3.6 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). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

One interim analysis for Study COU-AA-301 was planned after approximately 534 deaths were observed (67% of 797 total events) and a final analysis was planned after observing 797 total deaths. Clinical cut-off for the interim analysis was reached on 22 January 2010, at which time 552 deaths had been observed. Upon review of the interim efficacy data, the independent data monitoring committee (IDMC) concluded that the pre-specified efficacy boundary had been achieved and that there was significant benefit in OS for subjects receiving AAP. Based on these recommendations by the IDMC, the blinded portion of the study was terminated. The data from the 22 January 2010 interim analysis constituted the 'Primary' Analysis of COU-AA-301 and was reported in the Clinical Study Report (CSR) dated 2 December 2010 (CSR COU-AA-301 2010).[38] The 'Primary' Analysis formed the basis of the regulatory submissions. This interim analysis therefore became the 'Primary' analysis dataset.

A further follow-up analysis was conducted at 775 deaths (originally observed number required for the 'Primary' analysis). Subsequently, a Statistical Report[42] was then developed to provide an update to the data presented in the 'Primary' analysis CSR for key analyses on subject and treatment information, efficacy and safety. The clinical cut-off date for this update is 20 September 2010; no placebo subjects had crossed over to abiraterone acetate by this date.

Table 11 Summary of planned statistical analyses in COU-AA-301

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
COU-AA-301	The primary objective of the study is to compare the clinical benefit of AAP with PP in patients with mCRPC who have failed one or two chemotherapy regimens, one of which contains docetaxel.	Patient disposition and efficacy analyses were performed on data from the ITT population. The primary efficacy endpoint was OS, and was measured from the date of randomization to the date of death (whatever the cause). Survival time of living patients was be censored on the last date a patient is known to be alive or lost to follow-up. PSA response was scored in patients achieving a post-treatment PSA decline of at least 50% Time to PSA progression was measured from the time interval from the date of randomisation to the date of the PSA progression Radiographic PFS was measured from the date of randomisation to the first occurrence of radiographic progression or death. Safety analysis was summarised using the Safety Population.	The planned sample size of approximately 1158 patients (772 on abiraterone acetate and 386 on placebo) will provide 85% power to detect a difference between a median survival of 15 months in the AAP group and a median survival of 12 months PP group (HR=0.80) under the assumptions of a 2-tailed significance level of 0.05 and an enrolment of approximately 13 months over a total duration of approximately 30 months to obtain the required 797 total events. An interim analysis was planned after 534 death events were observed (67% of 797 total events) and a final analysis after observing the required 797 total events.	Survival data was captured regardless of whether the subject had discontinued treatment. Other endpoints were captured until treatment discontinuation as per time and events schedule. Reasons for patient discontinuation included: - Discontinuation of treatment criteria as defined in Section 6.8 - Dosing noncompliance - Sustained Side effects - Initiation of new anticancer treatment - Administration of prohibited medications - Patient withdraws consent

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

Subgroup analyses were carried out to assess if treatment effects are consistent within subgroup for the primary outcome. The HR within each subgroup was to be estimated using a Cox proportional hazards non-stratified model. Results from these analyses were to be considered consistent with the primary analysis if the 95% confidence interval (CI) for the HR within a subgroup included the point estimate for the primary analysis.

Subgroup analyses were planned for the primary endpoint OS to investigate whether or not treatment effects were consistent across subgroups. The following subgroups were pre-specified in the statistical analysis plan:[47]

- Type of progression: PSA only versus radiographic progression
- Subjects who entered the study with visceral disease
- Subjects whose baseline PSA concentration was greater than the median baseline concentration
- Subjects whose LDH concentration was greater than the median baseline concentration
- Subjects whose ALP concentration was greater than the median baseline concentration
- Region (North America versus non-North America)
- Subjects whose PSA concentration dropped at least 50% from the baseline

concentration
- Subjects who were considered a CTC responder.

The following subgroups were also explored as they were baseline stratification factors:
- ECOG performance status score: 0-1 versus 2
- Pain: BPI <4 or ≥4
- No of prior chemotherapy regimens: ‘One Prior Chemotherapy’ versus 2 or more different types of prior chemotherapy.

In addition, age was also explored in the subgroup analysis:
- Baseline age (<65, ≥65, ≥75 years).

Participant flow

5.3.8 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.

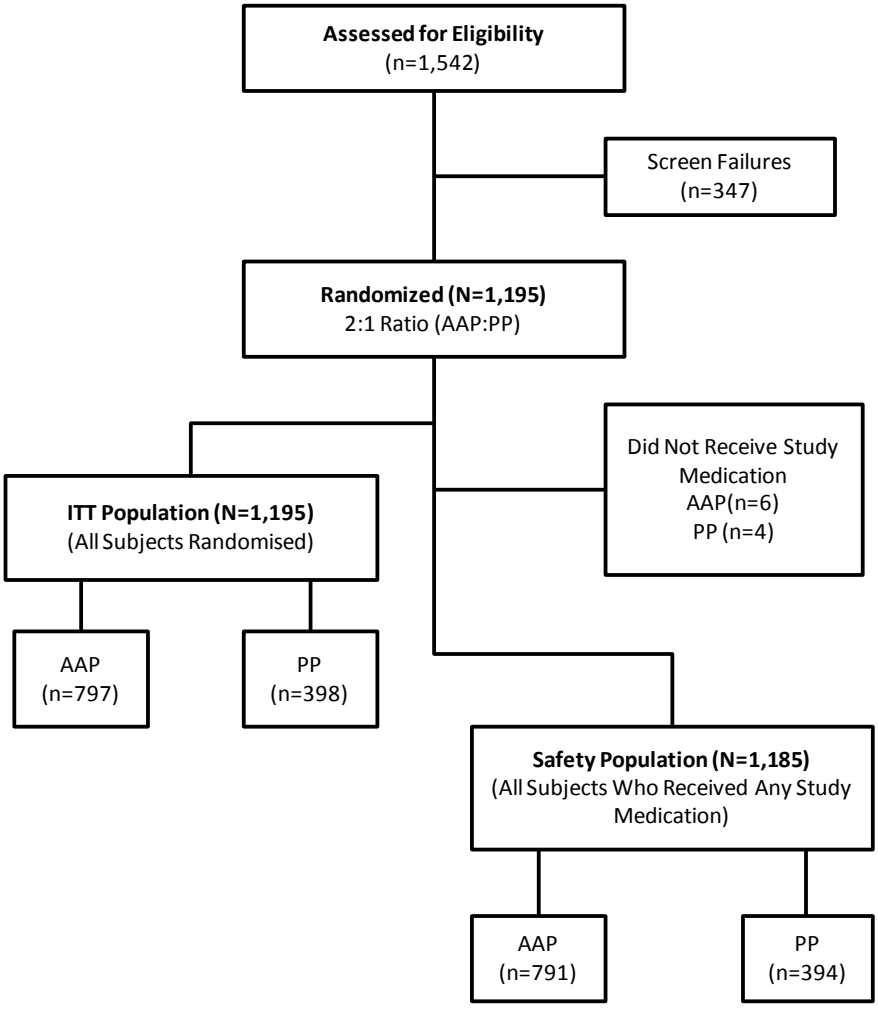


Figure 5 COU-AA-301 patient flow diagram. One subject was inadvertently randomised twice but is only counted once. AA=abiraterone acetate; ITT=intent-to-treat

The reasons for treatment discontinuation based on Sponsor medical review of the 'Updated' analysis time point (20.2 months median follow-up) are presented in Table 12. The most common reason for discontinuation was disease progression, although other reasons for discontinuation are also linked to disease progression (e.g. initiation of a new anticancer treatment and withdrawal of consent).

Table 12 Treatment discontinuations as per sponsor medical review, safety population.[f] 'Updated' analysis dataset (20.2 months median follow-up).[42]

	AAP (n = 791)	PP (n = 394)
Treatment ongoing	[redacted]	[redacted]
Treatment discontinued:	[redacted]	[redacted]
Due to disease progression	[redacted]	[redacted]
Other reason		
Initiation of new anticancer treatment	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Withdrawal of consent to treatment	[redacted]	[redacted]
Investigator discretion	[redacted]	[redacted]
Death	[redacted]	[redacted]
Other	[redacted]	[redacted]
Subject choice	[redacted]	[redacted]
Administration of prohibited medication	[redacted]	[redacted]
Dosing non-compliance	[redacted]	[redacted]
Placebo unblinding	[redacted]	[redacted]

5.4 Critical appraisal of relevant RCTs

5.4.1 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.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

A detailed quality assessment of COU-AA-301 is provided in Appendix 9.3.

f [redacted].

5.4.3 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.

Table 13 Quality assessment results for COU-AA-301

	COU-AA-301
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 imbalances in dropouts between groups were observed
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

5.5 Results of the relevant RCTs

5.5.1 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.

Results presented in the following section are based on the ITT results from the 'Primary' (12.8 month median follow-up) and the 'Updated' Analysis time point (20.2 months follow-up). Efficacy analyses were performed using the ITT population, which included all randomised subjects. For the cost-effectiveness of AAP to be estimated accurately, it is essential that the clinical data is externally valid and generalisable to the population of patients within England and Wales who are likely to receive AAP and should reflect the expected efficacy and underlying disease history within this population. Therefore, analyses for the population of patients with only 'One Prior Chemotherapy' regimen (n = 832, 70% of ITT) are also presented where available. The 'One Prior Chemotherapy' dataset (using the 'Updated' analysis) is the most relevant to the decision problem as it more accurately reflects the expected patient population within England and Wales for the following reasons:

- Use of a second or third chemotherapy regimen after 1st line docetaxel is not common in the UK (80% of patients currently only receive BSC immediately after docetaxel).[3] Docetaxel retreatment is not recommended by NICE guidelines[31]

- At the NICE scoping meeting for AAP in this indication, the consensus was that abiraterone acetate would be used prior to cabazitaxel (and other currently available 2nd line chemotherapy options). Therefore, in clinical practice in England

and Wales, AAP is more likely to be used following disease progression after only one line of chemotherapy (specifically one docetaxel regimen).

It should be noted that the 'One Prior Chemotherapy' population includes a proportion of subjects that may have received docetaxel re-treatment. It is not possible to calculate what proportion of subjects may have received docetaxel re-treatment due to the manner in which the data was collected in the CRF, so no further analysis based on lines of docetaxel is possible.

For the reasons stated above the clinical data most relevant to and reflective of the population of England and Wales is the 70% of patients that had only had 'One Prior Chemotherapy' regimen. Whilst results for both the ITT and the 'One Prior Chemotherapy' populations are presented in the following clinical section (where available), the population most similar to the expected population in England and Wales ('One Prior Chemotherapy' patients) is presented as the base case in the economic evaluation. Given that this descriptor was a stratification factor in the COU-AA-301 study, the baseline characteristics for the 'One Prior Chemotherapy' population are not different to the ITT population, Section 6.2, therefore there was no need to adjust for any baseline characteristics in subsequent analyses.

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

5.5.3 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.

5.5.3.1 Primary Outcome (OS)

Table 14 summarises the OS analyses from both the 'Primary' and 'Updated' time points. At the 'Updated' analysis time point, 775 (97%) of the planned number of events had occurred). A HR of 0.74 was observed at this time point (95% CI: 0.638, 0.859; p<0.0001). The median survival was significantly improved by 41% (15.8 months in the abiraterone acetate arm compared to 11.2 months in the prednisolone arm). [redacted]

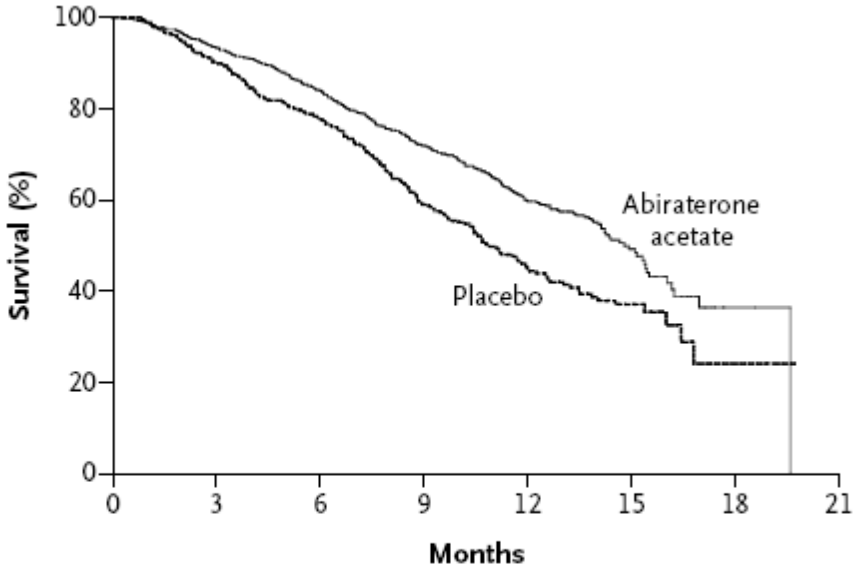
Median survival with AAP was extended by 4.6 months compared to PP, exceeding the ≥3months extension to life criterion set out in the Supplementary Advice on appraising End of Life medicines. The average life expectancy of patients in this indication is also less than 24 months; in the PP arm the median survival of patients was 11.2 months).

Table 14. OS of patients treated with either AAP or PP (ITT).

	AAP (N=797)	PP (N=398)
'Primary' Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value [a]	< 0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
'Updated' Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) [b]	0.740 (0.638, 0.859)	

[a]P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).

[b]Hazard ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favours Abiraterone acetate



No. at Risk								
Abiraterone acetate	797	736	657	520	282	68	2	0
Placebo	398	355	306	210	105	30	3	0

Figure 6. Overall survival for the ITT population ('Primary' Analysis).

[redacted]

[redacted]

Subgroup analyses

Detailed subgroup analysis was conducted at the 'Primary' analysis time point to examine the HRs for the risk of death, according to subgroup.[13] The effect on OS was found to be consistent across all subgroups (Figure 8).This subgroup analysis was only conducted at the 'Primary' time point, as when the pre-specified thresholds for the number of deaths were achieved at the interim time point, a full analysis of the dataset was conducted for regulatory purposes so that Accelerated Assessment Procedure could begin for abiraterone acetate. [redacted] Secondary endpoints were not explored in subgroup analyses at either time point. Analyses on exploratory biomarker endpoints (CTC and other potential biomarkers) have also been recently presented.[43] This biomarker analysis was conducted in a subgroup of 972 of the 1195 enrolled study patients. It was a post hoc analysis and CTC enumeration was not used in COU-AA-301 for individual patient management as investigators were blinded to CTC results.[g]

[g] CTC not currently used in routine clinical practice in the UK to assess disease progress. The COU-AA-301 study represents the first randomised controlled trial to evaluate CTCs as a potential surrogate biomarker for survival in metastatic prostate cancer. The aim of including CTCs in the study was to start the process of developing and validating a biomarker or biomarker panel which could be used in the future to accelerate the drug development process in prostate cancer.

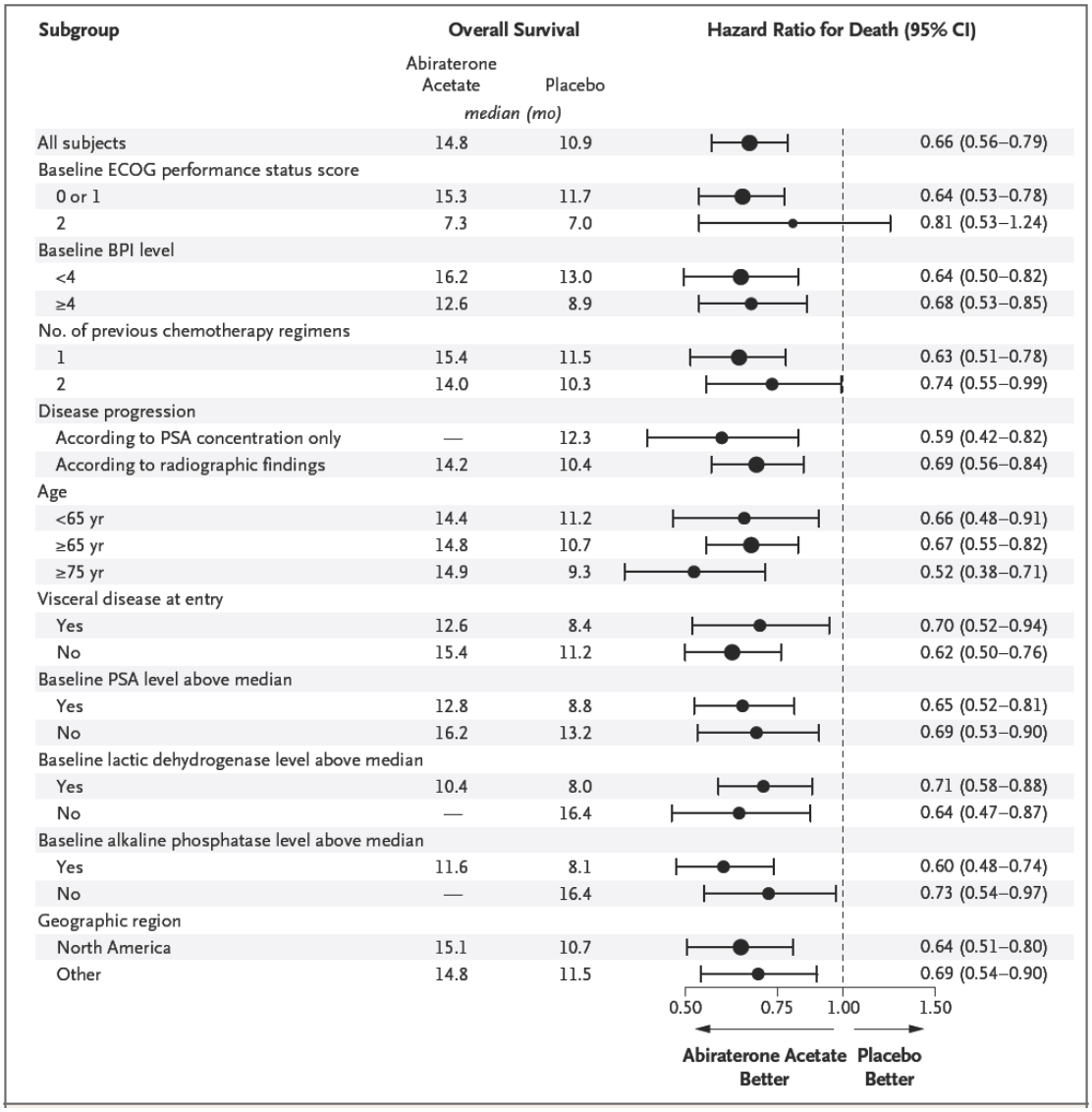


Figure 8. Hazard ratios based on a non-stratified proportional-hazards model[h] in COU-AA-301 study

[h] The ECOG grades the performance status of patients with respect to activities of daily living, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work; and 2 indicating that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities. Dashes indicate that the median time to death had not been reached for the indicated patient subgroup. The size of the circles is proportional to the size of the subgroup.

The decision problem specifies that three specific subgroups should be explored in this submission:

- baseline ECOG status
- extent of prior taxane exposure (reflected in the analysis as number of prior chemotherapy treatments)
- time since taxane treatment.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The 'One Prior Chemotherapy' population from COU-AA-301 has been explored further in the clinical analysis and is used in the base case of the economic analysis. [redacted] the 'One Prior Chemotherapy' population (70% of subjects in the COU-AA-301 study) is more likely reflective of the population in England and Wales that will receive abiraterone acetate as per the licence. Clinical opinion suggests that only a minority (20%) of UK mCRPC patients receive 2nd line chemotherapy treatments. Clinical outcomes for the 'One Prior Chemotherapy' population are presented where this analysis is available. [redacted]

[redacted]

5.5.3.2 Progression free survival, radiographic progression free survival and treatment discontinuation

Two PFS endpoints were pre-specified in the COU-AA-301 study: modified progression free survival (mPFS) and radiographic progression free survival (rPFS). rPFS was a secondary endpoint. [redacted]

Treatment with AAP significantly decreased the risk of radiographically documented disease progression or death by 33% compared with PP in the 'Primary' analysis (HR=0.673; 95% CI: 0.585, 0.776; p<0.0001) [redacted] The median rPFS was identical in both the 'Primary' and 'Updated' analyses:171.0 days (5.6 months) in the abiraterone acetate group and 110.0 days (3.6 months) in the prednisolone group. Therefore, regardless of PFS definition the hazard ratio is similar.

Two formal definitions of PFS were considered as secondary endpoints in the COU-AA-301 trial. Both of the PFS endpoints used in the trial were defined using a single assessment of disease progression; see Table 10 for full definitions. Oncologists actively treating prostate cancer in England and Wales, confirmed that disease progression in prostate cancer in clinical practice is not a decision made using any single assessment measure alone (e.g. radiographic or PSA progression alone). Therefore, the endpoints of mPFS and rPFS as defined in the trial do not represent when treatment with abiraterone acetate was necessarily discontinued in the trial due to disease progression. On this basis,

treatment discontinuation is the most appropriate proxy for PFS for use in the model; more detail on the rationale for this can be found in Section 6.3.1.

Treatment discontinuation curves are presented for the 'Primary' ITT analysis in Figure 10 and treatment discontinuation curves for both the 'Updated' ITT and 'One Prior Chemotherapy' population are presented in Figure 11 and Figure 12. The time to discontinuation of treatment was longer for the AAP arm compared to the PP arm at both 'Primary' and 'Updated' time points. Median time to treatment discontinuation in the 'Primary' analysis for AAP was [redacted]

[redacted]

In the 'Updated' analysis, the risk of discontinuation was significantly lower in the APP arm [redacted] in both the ITT and the 'One Prior Chemotherapy' population [redacted]

5.5.3.3 PSA response rate and time to PSA progression

In the 'Primary' analysis, the proportion of subjects with a confirmed PSA response of ≥50% decrease was significantly greater in the AAP group than in the PP group (29.1% versus 5.5%; p<0.0001). Total response (confirmed and unconfirmed[i]) was also greater in the AAP group than in the PP group (38.0% versus 10.1%; p<0.0001). In the 'Updated' analysis, the proportion of subjects with a confirmed PSA response was greater in the AAP group than in the PP group [redacted]. Total response (confirmed and unconfirmed) was also greater in the AAP group than in the PP group [redacted]These results are consistent with the three single arm studies reporting PSA response rates of between 36% and 51% for abiraterone acetate.[34-37]

PSA progression was documented in 32% and 30% of subjects in the AAP and PP groups, respectively, as PSA was only measured until treatment discontinuation, resulting in the censoring of data for a high proportion of subjects in both groups. In the 'Primary' analysis, treatment with AAP significantly decreased the risk of PSA progression by 42% compared with PP (HR=0.580; 95% CI: 0.462, 0.728; p<0.0001). The median time to PSA progression was 309.0 days (10.2 months) in the AAP group and 200.0 days (6.6 months) in the PP group. [redacted] Again, the hazard ratio reported for PSA progression was consistent with the hazard ratios reported for the different definitions of PFS.

5.5.3.4 Objective tumour response

Objective tumour response rate was assessed according to RECIST criteria. The proportion of subjects with measurable disease at baseline who had an objective response at the 'Primary' analysis point (all were partial response) was greater in the AAP group than in the PP group (14.0% versus 2.8%, p<0.0001). [redacted]

5.5.3.5 Circulating tumour cell response

Analysis on CTC responders was recently presented at ASCO 2011[43] and was conducted in a subgroup of 972 of the 1195 enrolled study patients. As noted earlier, this was a post hoc analysis and CTC enumeration was not used in COU-AA-301 for individual patient management as investigators were blinded to CTC results The results of the CTC analysis focus on a patient subgroup in the 'Updated' analysis dataset with CTC ≥5 at baseline and at least one post-baseline CTC value (n=422). At the four week time point significantly more AAP subjects (42%) had CTC conversion (CTC count went from ≥5 to <5) compared to PP subjects (14%), p<0.0001. At the 12 week time point (n=330) 48% of AAP subjects achieved CTC conversion compared to 17% of PP subjects, p<0.0001. These results are aligned with observations of CTC conversion from two single arm studies; reporting conversion rates of 36%[34] and 41%.[37].

[i] For a PSA response to be confirmed, an additional central laboratory measurement obtained 4 or more weeks later had to be a PSA concentration also showing at least a 50% decline from baseline.

5.5.3.6 Health related quality of life

In the statistical analysis plan for COU-AA-301, descriptive statistics were to be presented for each item collected for QOL. The FACT-P subscale scores (e.g., physical, social/family, emotional, functional well-being, and additional concerns) and total score were summarised descriptively by scheduled visit. Statistical analysis using paired t-tests were carried out to compare subsequent treatment visit scores with baseline score. Repeated measures analysis would also be employed as appropriate. Descriptive statistics for each item collected for the BFI-S and the BPI-S assessments were to be presented per visit (where appropriate). To supplement the initial analysis plan, detailed post-hoc analysis was conducted. Each of the three patient-reported outcome (PRO) measures was analysed to determine the proportion of subjects experiencing progression/degradation and palliation/improvement on each measure. The change thresholds were required to be maintained for two consecutive follow-up visits for the BPI-SF and Brief Fatigue Inventory-Short Form (BFI-SF) measures; however, since the Functional Assessment of Cancer Therapy – Prostate (FACT-P) was not measured at every cycle/visit, the change thresholds were only required to be met at one follow-up visit. The difference between treatment groups in median time to progression/degradation and palliation/improvement on each PRO measure was determined. All data reported below relating to these three PROs are from analyses on the 'Updated' dataset[44] as this is most relevant to the decision problem. Analyses from the 'Primary' analysis time point have been reported at recent conferences.[39, 41, 48]

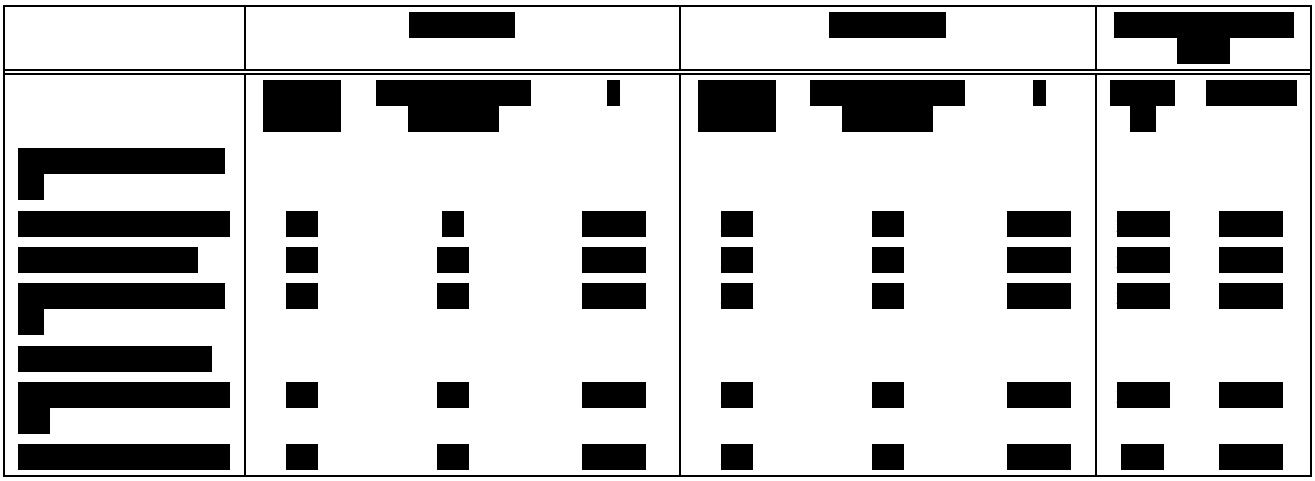
[redacted]

Table 16 [redacted]

[redacted]

[redacted]

Table 17. [redacted]



[redacted]

Table 18 [redacted]

[redacted]

The evidence from the COU-AA-301 study suggests that men receiving abiraterone are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens. The consistently favourable outcomes observed across the PROs assessed in this double-blind study are unusual to see for treatments in late stage metastatic cancers. This coupled with

the significant OS benefit and offers patients a tolerable treatment option with demonstrable survival benefit and favourable QoL in contrast to the very limited treatment options that are currently available.

5.5.3.7 Medical resource use

5.6 Meta-analysis

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

5.6.2 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.

A single RCT (COU-AA-301) was identified that compared abiraterone acetate with the most appropriate comparator, BSC, which is relevant to the decision problem in the post-chemotherapy patient population; therefore a meta-analysis was not undertaken. The summary of the evidence indentified during the systematic review for the other comparators is summarised in the following indirect comparison section (Section 5.7)

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (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.

Not applicable.

5.7 Indirect and mixed treatment comparisons

5.7.1 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 9.4, appendix 4.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The search strategy and methodology used to identify other clinical data on comparators relevant to the decision problem is described in Section 5.2. In addition to the COU-AA-301 study, the search identified nine further RCTs that included mitoxantrone + prednisolone or prednisolone or BSC. A list of these trials is provided below.

Table 19. Summary of RCTs identified during the systematic literature review.

Randomised controlled trials in metastatic CRPC	
Fleming, Kolodziej, Awasthi et al (2010)[49]	Cetuximab + mitoxantrone + prednisone vs. Mitoxantrone + prednisone
COU-AA-301 trial[13]	Abiraterone + prednisone +BSC vs. Prednisone + BSC
Ou, Michaelson, Sengelov et al., (2011)[50]	Sunitinib + prednisone vs. Prednisone
Salimichokami, Aminian, Ayati et al., (2010)[51]	Cyclophosphamide + thalidomide + dexamethasone vs. BSC
Saad, Hotte, North et al., (2008)[52]	Docetaxel + prednisone + custirsen vs. Mitoxantrone + prednisone + custirsen
Berger, Cluleanu, Hart et al., (2007)[53]	Irofulven + capecitabine + prednisone vs. Irofulven + prednisone vs. Mitoxantrone + prednisone
Rosenberg, Weinberg, Kelly et al., (2007)[54]	Ixabepilone vs. Mitoxantrone + prednisone
De Bono, Fizazi, Flechon et al (2010)[55]	CNTO 328 + mitoxantrone vs. Mitoxantrone
SPARC trial[56]	Prednisone vs. Satraplatin + prednisone
TROPIC study[12]	Cabazitaxel + prednisone vs. Mitoxantrone + prednisone

5.7.3 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.

The network of RCT evidence identified by the systematic review is described in Figure 13. There were no trials that compared mitoxantrone + prednisolone with prednisolone alone that would permit the direct or indirect comparison of these two comparators defined in the decision problem. Three trials[13, 50, 56] compared an investigational drug with prednisolone and four trials[12, 49, 53, 54] compared mitoxantrone + prednisolone with other investigational drugs. A further three studies were identified that compared treatment regimens in the population of interest; however none of these trials[51, 52, 55] were linked to the evidence network via treatments of interest.

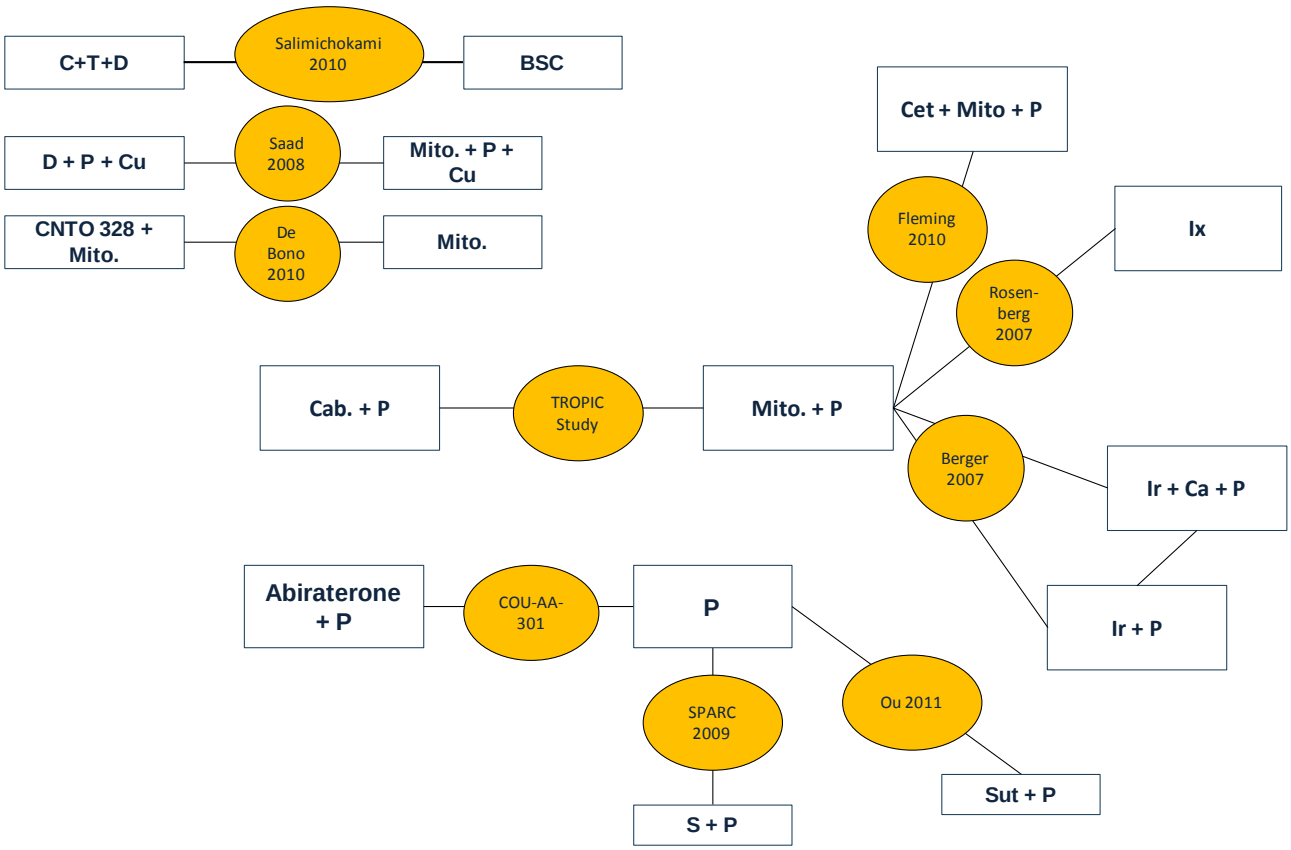


Figure 13. Schematic of the network of RCTs identified by the systematic review. Key: BSC = Best supportive care; Cab. = cabazitaxel; Ca = capecitabine; Cet = Cetuximab; C+T +D = Cyclophosphamide + Thalidomide + dexamethasone; Cu = custirsen; D = docetaxel; Ir = irofulven; Ix = ixabepilone; Mito. = mitoxantrone; P = prednisolone; S = satraplatin; Sut = sunitinib

The systematic review revealed a lack of direct and indirect evidence to link the comparators of interest in the post-chemotherapy patient population. The clinical benefits of mitoxantrone versus BSC in mCRPC patients previously treated with docetaxel has not been investigated, although a recent Phase III clinical trial evaluated mitoxantrone + prednisone versus cabazitaxel + prednisolone in patients with disease progression on docetaxel (de Bono et al. 2010[12]). Three trials of mitoxantrone + corticosteroid (prednisolone or hydrocortisone) versus corticosteroid have been conducted in chemotherapy naïve populations.[45, 57, 58] In these studies, mitoxantrone failed to demonstrate an OS benefit, but did show evidence of a palliative benefit in patients with mCRPC in terms of delayed time to progression and time to treatment failure, pain control, and PSA response rate. If mitoxantrone has failed to demonstrate an OS benefit over BSC in these chemotherapy naive populations, then it appears clinically implausible that it would confer a survival advantage in a population who have failed a previous chemotherapy and are therefore more resistant to treatment and potentially at greater risk of cumulative chemotherapy side effects. This is supported by clinical opinion. Due to the lack of direct or indirect evidence comparing mitoxantrone + prednisolone with prednisolone alone (to link mitoxantrone to the COU-AA-301 study), assumptions around OS, PFS and palliative benefits are explored in sensitivity analyses in the economic model.

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

Not applicable as an indirect comparison was not conducted.

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

Not applicable as an indirect comparison was not conducted.

5.7.6 Please present the results of the analysis.

Not applicable as an indirect comparison was not conducted.

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

Not applicable as an indirect comparison was not conducted.

5.7.8 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 an indirect comparison was not conducted.

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

Not applicable as an indirect comparison was not conducted.

5.8 Non-RCT evidence

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 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 9.6 and 9.7, appendices 6 and 7.

One overarching systematic review was conducted to identify all RCT and non-RCT evidence relevant to the decision problem. These methods have been previously described in Section 5.2. The systematic review identified 88 non-RCT studies in the post-chemotherapy patient population; 86 of these studies were single arm studies. Three single arm studies[34-37] explored outcomes associated with the administration of abiraterone, as previously summarised in section 5.2.8.

Of the six single arm studies that explored mitoxantrone regimens, only one study investigated the use of mitoxantrone in combination with prednisolone aligned with the decision problem.[59] The other mitoxantrone studies explored mitoxantrone in combination with other investigation drugs (ketoconazole, tesmilifene or ixabepilone) or mitoxantrone without prednisolone and are therefore not relevant to the decision problem. As all of the studies identified for interventions specified were single arm studies, none contributed to the evidence base relevant to the decision problem.

Table 20. Table of non-RCT studies identified by the systematic review involving comparators of interest.

Study	Intervention
Reid et al., (2010)[37]	Abiraterone
Logothetis et al., (2008)[36]	Abiraterone + prednisone
Danila et al., (2010)[34]	Abiraterone + prednisone
Efstathiou et al., (2010)[35]	Abiraterone + prednisone
Morales et al., (2010)[60]	Mitoxantrone
Ismail et al., (2010)[59]	Mitoxantrone + prednisone
Doshi et al., (2009)[61]	Ketoconazole + mitoxantrone + GM-CSF
Raghavan et al., (2005)[62]	Tesmilifene + mitoxantrone + prednisone
Osborne et al., (1983)[63]	Mitoxantrone
Small et al., (2009)[64]	Mitoxantrone + prednisone + ixabepilone

5.9 Adverse events

5.9.1 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 5.1 to 5.5 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 9.8 and 9.9, appendices 8 and 9.

The systematic review (methodology reported in section 5.2) identified one RCT (de Bono et al., (2011)[13]) and three single arm studies[34-37] containing data on AEs associated with abiraterone acetate administration. Reid et al., (2010) did not administer abiraterone acetate with prednisolone as per the label, so AEs from this study are not considered here.

5.9.2 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.

Summaries of AEs and other safety data are based on all subjects who were randomised and received any part of the study medication, i.e. the safety population. Within the COU-AA-301 study the proportion of subjects with AEs was similar between the two treatment

arms in all AE categories.[38, 42] At both the 'Primary' and 'Updated' time points, the abiraterone acetate arm had a lower incidence of Grade 3 or 4 AEs, serious AEs, AEs leading to discontinuation and AEs leading to death compared to the prednisolone arm.[38, 42] All AE results presented here are for all randomised subjects that received any study medication and not for the 'One Prior Chemotherapy' population.

AEs were also standardised for the duration of treatment exposure in the 'Updated' analysis. Three AEs were identified that may occur more frequently in the AAP group:

Table 21. Incidence of all adverse events occurring in more than 5% of patients across randomised groups in the COU-AA-301 at 'Primary' and 'Updated' analysis time points.

System organ / class / adverse events	'Primary' (12.8 months follow-up)			'Updated' (20.2 months follow-up)		
	AAP (%) (n = 791)	PP (%) (n = 394)	Relative risk (95% CI)	AAP (%) (n = 791)	PP (%) (n = 394)	Relative risk (95% CI)
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	233 (29.5%)	129 (32.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	215 (27.2%)	89 (22.6%)	[redacted]	[redacted]	[redacted]	[redacted]
Bone Pain	194 (24.5%)	110 (27.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	134 (16.9%)	79 (20.1%)	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Groin Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neck Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	346 (43.7%)	169 (42.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	197 (24.9%)	68 (17.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	104 (13.1%)	52 (13.2%)	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	71 (9.0%)	35 (8.9%)	[redacted]	[redacted]	[redacted]	[redacted]
Pain	<5%	<5%	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	233 (29.5%)	124 (31.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	206 (26.0%)	120 (30.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	168 (21.2%)	97 (24.6%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	139 (17.6%)	53 (13.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	135 (17.1%)	33 (8.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	91 (11.5%)	28 (7.1%)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	102 (12.9%)	46 (11.7%)	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Vascular disorders						
Hot Flush						
Hypertension	67 (8.5%)	27 (6.9%)				
Investigations						
Weight decreased						
Renal and urinary disorders						
Haematuria	65 (8.2%)	31 (7.9%)				
Pollakiuria						
Nocturia						
Urinary retention						
Blood and lymphatic disorders						
Anaemia	178 (22.5%)	104 (26.4%)				
Psychiatric disorders						
Insomnia						
Anxiety						
Depression						
Skin and subcutaneous tissue disorders						
Hyperhidrosis						
Injury, poisoning and procedural complications						
Contusion						
Reproductive system and breast disorders						
Pelvic pain						

CI, confidence interval

Adapted from European Public Assessment Reports published by the European Medicines Agency

At the ‘Primary’ time point, across both groups, the most frequently reported AEs were fatigue (44% and 43% in the abiraterone acetate and placebo groups, respectively), back pain (30% and 33%, respectively), nausea (30% and 32%, respectively), and constipation (26% and 31%, respectively), consistent with the natural history of mCRPC. Most of these events were Grade 1 or 2. Urinary tract infection, was more frequent in the abiraterone acetate group than in the placebo group (12% versus 7%); but these were primarily Grade 1 or 2 events. The incidence of individual AEs did not increase by more than 4% for any treatment arm between the ‘Primary’ and ‘Updated’ analysis time points.

At the ‘Primary’ time points, across both groups, the most frequently reported Grade 3 or 4 AEs were fatigue (8% and 10% in the abiraterone acetate and placebo groups, respectively), anaemia (8% and 7%, respectively), back pain (6% and 10%, respectively), and bone pain (6% and 7%, respectively). No individual Grade 4 AEs occurred in more than 2% of subjects in either group. The incidence of individual Grade 3 or 4 AEs did not increase by more than 2% for any treatment arm between the ‘Primary’ and ‘Updated’ analysis time points.

AEs of special interest, which include events related to mineralocorticoid excess (hypertension, hypokalaemia, and fluid retention/oedema), cardiac disorders, and hepatotoxicity, were also reported. AEs of special interest were reported in a higher proportion of subjects in the abiraterone acetate group than in the placebo group (55% versus 44%). Fluid retention/oedema was reported in 31% of subjects in the abiraterone

acetate group and 22% of subjects in the placebo group; however Grade 3 or 4 peripheral oedema was low and similar between groups (2% AAP vs. 1% PP). Hypokalaemia was reported in 17% of subjects in the AAP group and 8% of subjects in the PP group, with low numbers of Grade 3 or 4 hypokalaemia 4% AAP vs. 1% in both groups. Hypertension events occurred in 10% of subjects in the abiraterone acetate group and 8% of subjects in the placebo group, while (Grade 3 or 4 hypertension was low and similar between groups (1.3% AAP vs. 0.3% PP).

Cardiac disorders occurred in 13% of subjects in the abiraterone acetate group and 11% of subjects in the placebo group. The most frequently reported cardiac disorder events were tachycardia (3% and 2% of subjects in the abiraterone acetate and placebo groups, respectively) and atrial fibrillation (2% and 1%, respectively). The incidence of myocardial infarction was 0.8% in both groups. Cardiac failure was reported in 2% of subjects in the abiraterone acetate group and 1% of subjects in the placebo group. No Grade 3, 4, or 5 tachycardia events were reported in either group. Grade 3 atrial fibrillation events were reported in 1% of subjects in both groups.

AEs reported as hepatotoxicity AEs were observed in 10% of subjects in the abiraterone acetate group and 8% of subjects in the placebo group. The most frequently reported individual AEs were increases in ALP and AST (4% of subjects in both groups), increased ALT (3% and 1% of subjects in the abiraterone acetate and placebo groups, respectively), and hyperbilirubinemia (1% and 2% of subjects in the abiraterone acetate and placebo groups, respectively). Grade 3 or 4 ALP increase similar between groups, 1% of subjects in the AAP group and 2% of subjects in the PP group. Grade 3 or 4 AST increase occurred in 1% of subjects in both groups. Grade 3 ALT increase was reported in 0.9% of subjects in the abiraterone acetate group, with no Grade 4 events reported; 0.5% of subjects in the placebo group had Grade 3 or 4 events. Grade 3 hyperbilirubinemia was reported in 0.4% of subjects in the abiraterone group, with no Grade 4 events reported; 0.8% of subjects in the placebo group had Grade 3 or 4 events.

Table 22. Incidence of grade 3 or 4 adverse events occurring in more than 1% of patients across randomised groups in the COU-AA-301 at 'Primary' and 'Updated' analysis time points.

System organ/ class/adverse events	'Primary' (12.8 months follow-up)			'Updated' (20.2 months follow-up)		
	AAP (%) (n = 791)	PP (%) (n = 394)	Relative risk (95% CI)	AAP (%) (n = 791)	PP (%) (n = 394)	Relative risk (95% CI)
Total	**431 (54.5%)**	**230 (58.4%)**				
Musculoskeletal and connective tissue disorders	**155 (19.6%)**	**96 (24.4%)**				
Back pain	47 (5.9%)	38 (9.6%)				
Bone Pain	44 (5.6%)	29 (7.4%)				
Arthralgia	33 (4.2%)	16 (4.1%)				
Musculoskeletal pain	21 (2.7%)	8 (2.0%)				
Pain in extremity	19 (2.4%)	20 (5.1%)				
Muscular weakness	18 (2.3%)	5 (1.3%)				
Pain	<1%	<1%				
General disorders and administration site conditions	**116 (14.7%)**	**64 (16.2%)**				
Fatigue	66 (8.3%)	39 (9.9%)				
Asthenia	18 (2.3%)	8 (2.0%)				
Disease Progression	13 (1.6%)	2 (0.5%)				

Oedema peripheral	12 (1.5%)	3 (0.8%)	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	8 (1.0%)	2 (0.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Pain	5 (0.6%)	7 (1.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	3 (0.4%)	5 (1.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	**94 (11.9%)**	**42 (10.7%)**	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	30 (3.8%)	3 (0.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	19 (2.4%)	7 (1.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	13 (1.6%)	6 (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Anorexia	12 (1.5%)	12 (3.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	11 (1.4%)	3 (0.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypophospataemia	11 (1.4%)	3 (0.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycaemia	2 (0.3%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	1 (0.1%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic disorders	**71 (9.0%)**	**34 (8.6%)**	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	59 (7.5%)	29 (7.4%)	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	11 (1.4%)	2 (0.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	**65 (8.2%)**	**52 (13.2%)**	[redacted]	[redacted]	[redacted]	[redacted]
Spinal cord compression	22 (2.8%)	20 (5.1%)	[redacted]	[redacted]	[redacted]	[redacted]
Headache	8 (1.0%)	3 (0.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	**64 (8.1%)**	**32 (8.1%)**	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	16 (2.0%)	6 (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	14 (1.8%)	11 (2.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	13 (1.6%)	10 (2.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	8 (1.0%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	5 (0.6%)	5 (1.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	<1%	<1%	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	**63 (8.0%)**	**21 (5.3%)**	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	17 (2.1%)	2 (0.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	14 (1.8%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	<1%	<1%	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	**52 (6.6%)**	**24 (6.1%)**	[redacted]	[redacted]	[redacted]	[redacted]
Hydronephrosis	13 (1.6%)	2 (0.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria	11 (1.4%)	9 (2.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	8 (1.0%)	6 (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary incontinence	<1%	<1%	[redacted]	[redacted]	[redacted]	[redacted]
Renal failure acute	7 (0.9%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Renal Failure	<1%	<1%	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	**47 (5.9%)**	**16 (4.1%)**	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	11 (1.4%)	6 (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	<1%	<1%	[redacted]	[redacted]	[redacted]	[redacted]
Asparatate aminotransferase increased	8 (1.0%)	4 (1.0%)	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	2 (0.3%)	5 (1.3%)	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	**29 (3.7%)**	**5 (1.3%)**	[redacted]	[redacted]	[redacted]	[redacted]

Hypertension	10 (1.3%)	1 (0.3%)	[redacted]			
Deep vein thrombosis	<1%	<1%	[redacted]			
Hypotension	8 (1.0%)	2 (0.5%)	[redacted]			
Respiratory, thoracic and mediastinal disorders	**25 (3.2%)**	**21 (5.3%)**	[redacted]			
Dyspnoea	10 (1.3%)	9 (2.3%)	[redacted]			
Pulmonary embolism	3 (0.4%)	9 (2.3%)	[redacted]			
Hepatobilliary disorders	**<1%**	**<1%**	[redacted]			
Hyperbilirubinaemia	<1%	<1%	[redacted]			
Psychiatric disorders	**18 (2.3%)**	**7 (1.8%)**	[redacted]			
Confusional state	4 (0.5%)	4 (1.0%)	[redacted]			
Reproductive system and breast disorders	**7 (0.9%)**	**10 (2.5%)**	[redacted]			
Pelvic pain	3 (0.4%)	10 (2.5%)	[redacted]			

CI, confidence interval

Adapted from European Public Assessment Reports published by the European Medicines Agency

Separate AE analyses for the 'One Prior Chemotherapy' population have not been conducted, as there is no biologically plausible reason that this population would have a differing rate of AEs compared to the ITT population. Indeed, it might be possible that those less heavily treated patients would be less likely to experience AEs.

The EPAR concluded that the safety profile of abiraterone acetate was considered acceptable and generally manageable with basic medical interventions. Toxicities were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations. In this regard it should be noted that the safety profile of abiraterone acetate is distinct from that typically induced by conventional cytotoxic agents, which is frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, or life-threatening. Indeed, AEs such as hypertension or hypokalaemia are generally asymptomatic, and although fluid retention/oedema or urinary tract infections may be more disturbing to the patient, abiraterone does not induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia, alopecia, etc, which not only may be associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life which is particularly relevant in the context of non-curative therapy for an end-stage disease[15]).

The time to first skeletal related AEs was also assessed as a pre-specified efficacy endpoint of particular interest. SREs are a consequence of metastatic disease and have significant impact on patient quality of life[10] and costs[65], see sections 6.4.1 and 6.5.3. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. [redacted]

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

The EPAR concluded that the safety profile of abiraterone acetate is considered acceptable and generally manageable with basic medical interventions. Of particular note, individual grade 3/4 AEs of special interest (hypertension, hypokalaemia, fluid retention/oedema, cardiac disorders, and hepatotoxicity) were low and did not occur in more than 4% of abiraterone patients.

The safety profile of abiraterone acetate is therefore differentiated from conventional cytotoxic agents (mitoxantrone and docetaxel) that are frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, or life-threatening. Abiraterone acetate does not induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia and alopecia. These toxicities induced by cytotoxic chemotherapies, are not only associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life which is particularly relevant in the context of non-curative therapy for an end-stage disease.

5.10 Interpretation of clinical evidence

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

The primary clinical aims of treating mCRPC are to improve survival, delay disease progression and maintain patient quality of life for as long as possible. Abiraterone acetate contributes to these survival, disease progression and quality of life goals. The treatment is generally well tolerated and rarely associated with debilitating AEs and most patients' quality of life is improved or maintained whilst on treatment. In addition, patients experience a reduction in pain, decreased fatigue and an improved functional status.

The primary clinical benefit of abiraterone acetate is that it significantly improves median OS by 41% (20.2 months median follow-up) compared to PP. Median survival was 3.9 months longer in the AAP arm compared to PP arm (14.8 (95% CI 14.1, 15.4) vs. 10.9 (95% CI 10.2, 12.0) at the 'Primary' time point and 4.6 months longer at the 'Updated' analysis time point (15.8 (95% CI 14.8, 17.0) vs. 11.2 (95% CI 10.4,13.1)). This treatment effect on OS remains significant after adjusting for stratification factors and across subgroups in a multivariate analysis. Furthermore, men receiving abiraterone acetate are more likely to have better quality of life, whilst also experiencing improvement in survival. They are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens. It should be noted that the consistently favourable outcomes observed across the PROs assessed in this double-blind study are unusual to see for treatments in late stage metastatic cancers.

AEs associated with taking abiraterone acetate are mild to moderate in nature, generally manageable and reversible with basic medical interventions. Of note, the incidence of individual grade 3 or 4 individual AEs is low and do not exceed 10% in the abiraterone arm of the study. The incidence of individual grade 3 or 4 AEs of special interest (hypertension, hypokalaemia, fluid retention/oedema, cardiac disorders, and hepatotoxicity) was also low, not exceeding 4%.

Abiraterone acetate has been developed to target the second leading cause of death in men in the UK; prostate cancer deaths account for 12.5% of all male cancer mortality.[66] Abiraterone acetate is novel, first in class, oral therapy that inhibits testosterone production

at all three sites in the body (tumour, testes and adrenal glands). The novel mechanism of action and clinical outcomes observed with abiraterone acetate has necessitated the creation of a separate category within the LO2BX class of agents by the World Health Organisation International Working Group for Drug Statistics Methodology. The new ATC code will be L02BX03 “Other hormone antagonists and related agents”.

Currently, patients with mCRPC have few treatment options after 1st line docetaxel treatment. Abiraterone acetate offers a step change to the treatment pathway, as it offers a treatment option to mCRPC patients whose only current options include best supportive care or 2nd line chemotherapy, for which the risk/benefit analysis is unknown. The risk benefit/profile of abiraterone acetate has been deemed very positive and led to the accelerated approval within this indication. In addition, the maintenance of quality of life alongside the delay in SREs may keep patients more mobile and active.

In summary, abiraterone acetate offers mCRPC patients an oral treatment that significantly increases their life expectancy and delays disease progression without compromising quality of life.

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

A single Phase III study, COU-AA-301, has been conducted to explore the efficacy and safety of abiraterone acetate, and this trial has been considered to be of high quality, mature, robust, consistent and clinically relevant.[15] These results are supplemented by several smaller Phase II single arm studies, which are aligned with the outcomes observed in the primary study. The COU-AA-301 study was a large multi-centre, multi-country study in nearly 1200 subjects in the population granted the European licence. COU-AA-301 involved 178 patients from 12 UK sites, making the study results particularly relevant to the UK population. In addition, PP is the primary comparator relevant to the decision problem.

One of the limitations of COU-AA-301 was that the ITT population contained a higher proportion of patients with two or more lines of chemotherapy than is observed in the UK population; 30% of the patients in COU-AA-301 had 2 or more prior chemotherapies. Clinical and economic analyses have therefore explored the outcomes for the 70% of the COU-AA-301 only exposed to ‘One Prior Chemotherapy’ regimen and these results are presented as the model base case.

5.10.3 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.

The Phase III clinical trial (COU-AA-301) is directly related to the decision problem as this study directly compares abiraterone acetate to the main comparator of interest, PP. This trial did not include a comparison with the chemotherapy comparator included in the decision problem (MP); however clinical opinion suggests that MP is not commonly used in current UK clinical practice in this post-docetaxel population (only in approximately 10% of patients).

The clinical results have been presented for the ‘One Prior Chemotherapy’ population, where available, as this population better reflects the population that will be prescribed abiraterone acetate in UK clinical practice. Baseline characteristics for the ‘One Prior Chemotherapy’ population were very similar to those of the ITT population. UK patients on

abiraterone acetate will therefore experience a significant improvement in survival of [redacted]. Patients taking abiraterone acetate can also expect a longer time prior to disease progression ([redacted]) compared to currently available treatment options. Although analyses for the 'One Prior Chemotherapy' subgroup have not been conducted for other endpoints, the results observed for the ITT population, with respect to PSA and tumour response, as well as HRQL should be expected to be similar in the UK population. Patients receiving abiraterone acetate should expect to improve of maintain quality of life whilst experiencing improvement in survival; specifically reduced pain, improved functional status, decreased fatigue and a delay in time to SREs.

5.10.4 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?

Janssen does not anticipate that the study results observed in the clinical trials will differ from the use of abiraterone acetate in clinical practice within the NHS. Twelve UK sites (172 UK patients) were included as part of the study and clinical opinion suggests that clinical benefits and safety profile demonstrated within the clinical trial are not likely to differ from those expected in UK clinical practice. The dose of abiraterone acetate used in the clinical trial (and in the SPC) is identical to the dose that will be used in UK clinical practice.

As mentioned in Section 5.10.2, the ITT population from COU-AA-301 is not thought to best reflect the UK population, due to the higher proportion of patients with two of more lines of prior chemotherapy. In the UK, chemotherapy retreatment is less common than in other countries and therefore the subpopulation (70%) of those patients with 'One Prior Chemotherapy' regimen is more reflective of the licence as it would be applied in the UK.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 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 9.10, appendix 10.

A full systematic review of the literature, using one overarching strategy, was conducted to identify all primary studies in advanced or metastatic prostate cancer that involved an economic evaluation, a burden of illness study or an evaluation linked to an HTA submission.

Literature databases (MEDLINE (including MEDLINE In-Process, Other Non-Indexed Citations), Excerpta Medica Database (EMBASE), Cochrane: Economic Evaluation and Technology Assessments databases and EconLit) were searched to identify studies published between 1st January 2000 to 10th June 2011. Standard filters based on those developed by the Scottish Intercollegiate Guidance Network (SIGN)[67] were used to identify economic studies in Medline and Embase. Clinical keywords and medical subject headings were used to search for disease and interventions, and these are fully explained in Appendix 10. To supplement the review, the conference proceedings and journals from ISPOR International (2006-2010) and ISPOR European (2006-2011) were hand searched.

To be included in the review, studies had to meet pre-defined eligibility criteria pre-specified in the systematic review protocol. Only English language studies were included. Inclusion criteria for the review are detailed in Table 23.

Table 23. Inclusion criteria for economic evaluation systematic review.

Studies to include		Rationale
Study designs	Budget impact analyses, Resource use studies, Cost/economic burden of illness studies, Cost analyses, Cost-minimisation analyses, Cost-effective analyses, Cost-utility analyses, Cost-benefit analyses, Clinical trial-based analyses	These types of economic studies were seen a potential sources to input into the development of the economic model relevant to the decision problem.
Population	Adults (≥ 18 years), Males, Any race, Confirmed diagnosis of advanced or metastatic prostate cancer All lines of therapy	Only studies relating to advanced or metastatic prostate cancer were relevant to the decision problem.
Interventions	5-FU, abarelix abiraterone acetate Aflibercept Aminoglutethimide AS1404, Atrasentan Bevacizumab, bicalutamide CAB, Cabazitaxel Carboplatin cyproterone acetate Dasatinib, degarelix dexamethasone diethystilbesterol Docetaxel, Doxorubicin dutasteride e7389/ eribulin mesylate estramustine, Etoposide Finasteride, flutamide goserelin hydrocortisone IMC-A12 Ipilimumab, JM216 ketoconazole leuprorelin, mdv3100 megestrol Mitoxantrone Nilutamide, Paclitaxel Pamidronate, Patupilone Prednisone, samarium sipuleucel T strontium, Sunitinib TAK-700, triptorelin Vinblastine, Vinorelbine zd4054 Zoledronic acid	All commonly used interventions in mCRPC were included in the search. All of these interventions in combination or as monotherapy.
Language	English language only	

Bibliographic details and abstracts of all citations identified by the literature search were downloaded into a bespoke, SQL-based internet database. Citations were first screened by a single reviewer based on the abstract supplied with each citation. Those that did not match the eligibility criteria were excluded at this 'first pass'. All decisions were checked by a second reviewer. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. Full-text copies of all references that could potentially meet the eligibility criteria were ordered at this stage. In instances when it was not possible to include or exclude citations based on the abstract, full-text copies were obtained. The eligibility criteria were applied to the full-text citations, and the data presented in the studies still included after this stage were extracted to data extraction grids. This stage was performed by a single reviewer with decisions checked by a second reviewer.

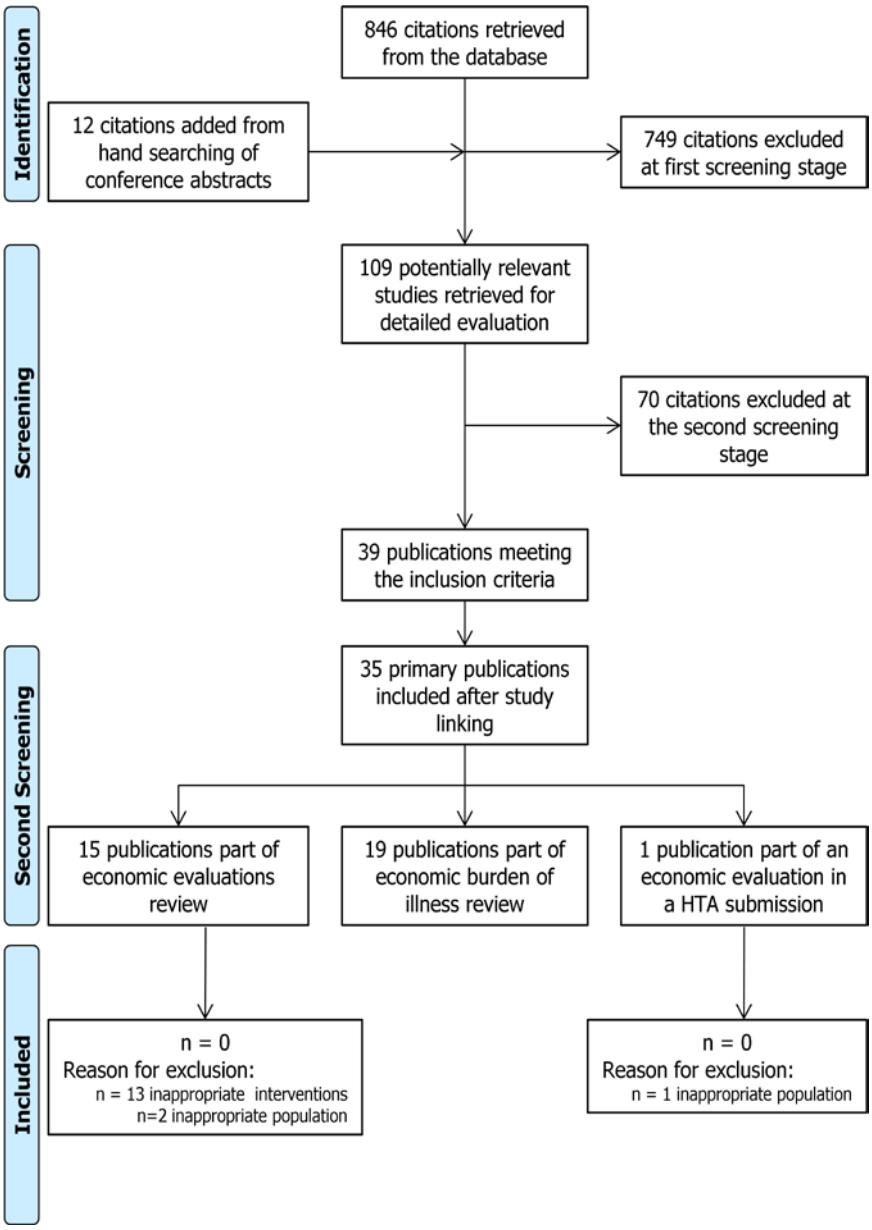


Figure 14. Study exclusion flow for economic systematic review

Description of identified studies

6.1.2 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.

The systematic literature review identified 15 economic evaluations and one additional economic evaluation associated with an HTA appraisal. None of the studies identified was directly related to the decision problem. Thirteen studies were excluded due to inappropriate interventions and a further three studies were excluded as they did not explore a population relevant to the decision problem, Table 24.

Table 24. Summary list of other cost-effectiveness evaluations that were excluded as they were not relevant to the decision problem.

Study	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)
Aprikian et al., (2003)[68]	Canada	CEA, calculation based on published clinical trial data, perspective unclear, timeframe length of treatment, no discounting	Not reported	No QALYs reported. Castration vs. castration + NSAA	Cost of bicalutamide used for calculation; $193.20/month	Cost per month of survival gain for CAB vs. castration alone ranged from $437 to $1107 per month
Bayoumi et al,. (2000)[69]	United States	CEA, Markov model, societal perspective, timeframe 20 years, 3% discount rate for costs and QoL weights	Base case assumption 65 years	DES: 4.64 Orchiectomy: 5.10 NSAA: 4.98 NSAA+orchiectomy: 5.05 LHRH agonists: 5.08 NSAA + LHRH agonists: 5.03	DES: 3600$ Orchiectomy: 7000$ NSAA: 16,100$ NSAA+orchiectomy: 20,700$ LHRH agonists: 27,000$ NSAA + LHRH agonists: 40,3000$	DES: Referent Orchiectomy: 75000$/QALY NSAA: dominated NSAA+orchiectomy: dominated LHRH agonists: dominated NSAA + LHRH agonists: dominated *Cost in 1998 US Dollar*
Carter (2011)[70]	France, Germany, Portugal, and the Netherlands	CEA/CUA, decision-analytic model, payer perspective, timeframe 15 months, no discounting	Mean age 71.8 years (+/-7.9) within the zoledronic acid and placebo arms of the RCT	Zoledronic acid vs placebo 0.03566 QALYs	Incremental total costs per country, Zoledronic acid vs placebo:	Cost/QALY per country, Zoledronic acid vs placebo:
Chau (2010)[71]	Canada	CEA, population-based, retrospective analysis, no modelling	Mean age 72.7 years	Not reported	Incremental cost: CAB vs ADT: 1,248,599 CAN$	CAB vs ADT: $11,220 per LYG
Collins et al., (2007*)[72]	UK	CEA, Markov model, NHS perspective, timeframe 15 years, 3.5% discount rate for both costs and health outcomes	NR; starting age approx. 68 years	Prednisolone (P): 0.81001 Mitoxantrone + Prednisolone (M + P): 0.81364 Docetaxel + Prednisolone (D+P) (3 weekly): 0.96801	Estimated mean lifetime costs P: £11,227 M + P: £10,834 D + P (3 weekly): £15,883	P: dominated M + P: - D + P (3 weekly): £32,706/QALY
Iannazzo et al., (2009)[73] *(abstract)*	Italy	CUA, Markov model, third party payer perspective (Italian NHS), timeframe lifetime, discounting unclear	Not reported	QALYs ranged from 9.98 for MAB to 9.28 QALYs for NSAA-flutamide	Cost per patient varied between 12,538 € for orchiectomy to 59,496 € for NSAA-bicalutamide	Orchiectomy most cost effective alternative with 1,300 €/QALY, leuprorelin most cost effective LHRA agonist with 2,200 €/QALY
Iannazzo et al., (2011)[74]	Italy	CEA, Patient level, microsimulation decision tree model leading to a Markov model, third party payer perspective (Italian NHS), timeframe not reported, 3.5% discount	Not reported	No QALYs reported. OS/PFS (SD) per LHRA agonist: Leuprorelin 22.5mg: OS 60.31 (34,09), PFS 40.49 (41.42) Leuprorelin 11.25mg: OS 59.49	Total costs (SD): Leuprorelin 22.5mg: 13,981 € (5,150) Leuprorelin 11.25mg: 15,114 € (5,502)	Incremental cost per month of life gained vs/ Leuprorelin 22.5mg: Leuprorelin 11.25mg: dominated Goserelin: dominated Triptorelin: dominated

		rate for both costs and survival outcomes		(33.75), PFS 34.86 (40.86) Goserelin: OS 57.93 (32.93), PFS 38.40 (39.22) Triptorelin: OS 59.87 (33.99), PFS 40.19 (41.17) Buserelin: OS 60.35 (34.15), PFS 40.57 (41.55)	Goserelin: 16,579 € (6,133) Triptorelin: 15,935 € (5,909) Buserelin: 14,546 € (5,277)	Buserelin: 11,700 €
Konski et al., (2004)[75]	United States	CUA, Markov model, third party payer/Medicare perspective, timeframe 24 months, no discounting	Not reported	Pain medication: 5.75 SFX: 6.1 MFX:6.25 Chemotherapy:4.93	Incremental cost: Pain medication: - SFX: $200 MFX:$1,500 Chemotherapy:$3,600	Pain medication: - SFX: $6,857 MFX:$36,000 Chemotherapy: dominated
Nygard et al., (2001)[76]	Norway	Assessment of QoL and cost, cohort model, third party payer perspective, timeframe 36 months, 5% discount rate	Median age 73 years	Mean QoL: 15D (0-100) Orchiectomy: 76 LHRH analogues: 72 EORTC QLQ-C30 (0-100) Orchiectomy: 63 LHRH analogues: 49	Treatment costs for 36 months: Orchiectomy: £8,895 LHRH analogues: £10,937	Not reported
Odeyemi et al., (2007)[77]	Germany	CMA, decision tree model, third party payer perspective, timeframe 12 months, no discounting	Mean age between 72,8 years (1-monthly dosage), 73.1 years (3-monthly dosage), 73.2 years (6-monthly dosage)	Not reported (CMA)	Mean annual treatment cost per formulation: 1-monthly dosage:2,839 € 3-monthly dosage: 1,777 € 6-monthly dosage: 1,567 €	Not reported (CMA)
Penson et al., (2005)[78]	Not reported; presumably United States	CEA, decision tree model, third party payer perspective, timeframe 5 and 10 years, 3% discount rate	Any age	Not reported	Not reported	CAB+ bicalutamide vs. LHRAa alone 5 years: $33,677 per QALY 10 years: $20,053 per QALY
Ramsey et al., (2005)[79]	United States	CEA, decision tree model, third party payer perspective, timeframe 60 months and 120 months, 3% discount rate	Not reported	Median time to progression: Bicalutamide+LHRH: 97 weeks LHRH: 77 weeks	Not reported	ICER at 60 months: Bicalutamide (+LHRH agonist) vs. flutamide (+LHRH agonist): $22,000
Reed et al., (2004)[80]	Argentina, Austria, Australia, Belgium, Brazil, Canada, Chile, France, Germany,	CUA, patient level simulation, societal perspective (direct costs only), timeframe 15 months, no discounting	Median age (patients with resource use data): 73 years; (patients without resource	Not reported; average incremental gain in quality adjusted time during study period approx 2 weeks for patients receiving zoledronic	Average within-trial costs per patient; total medical costs excluding study medication: Zoledronic acid: $5,365 Placebo: $5,689	Zoledronic acid vs. placebo: $159,200

	Italy, New Zealand, Peru, Sweden, Switzerland, UK, US, Uruguay		use data: 70 years)	acid		
Wex et al., (2011) (PCN64)[81] *(abstract)*	Belgium	CMA, excel model not further specified, public payer perspective, timeframe 12 months, no discounting	Not reported	Not reported (CMA)	Treatment cost: Leuprolide 1-montly (1M): 3,746 € Leuprolide 3-monthly (3M): 1,739 € less costly than 1M Leuprolide 6-monthly (6M): savings of 2,126 € compared to 1M	Not reported (CMA)
Wex et al,. (2011) (PCN65)[82] *(abstract)*	Portugal	CMA, excel model not further specified, public payer perspective, timeframe 12 months, no discounting	Not reported	Not reported (CMA)	Treatment cost: Leuprolide 1-montly (1M): 4,597 € Leuprolide 3-monthly (3M): 11,788 € less costly than 1M Leuprolide 6-monthly (6M): savings of 2,230 € compared to 1M	Not reported (CMA)

CAB=combined androgen blockade; DES = diethylstilbestrol; LHRH = luteinizing hormone-releasing hormone; MAB = maximal androgen blockade; MFX = multifraction; NSAA = nonsteroidal antiandrogen; SFX = single fraction.

6.1.3 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)[j] or Philips et al. (2004)[k]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Not applicable.

6.2 De novo analysis

Patients

6.2.1 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 1.4 and 5.3.3, 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.

Abiraterone acetate is indicated with prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The base case focuses on the patients who have received only 'One Prior Chemotherapy' regimen. Patients who had more than 'One Prior Chemotherapy' regimen are not considered in the base case. To inform the analysis, the base case model uses data from the 'Updated Analysis' of the COU AA 301 study for the subset of patients who had received one prior docetaxel-based chemotherapy regimen. Whilst the majority of this group will have received one prior course of Docetaxel, a proportion could have had repeated courses of docetaxel prior to enrolment into the study. However, due to the manner in which data was captured in the case report form, the exact proportion of men in COU-AA-301 who had docetaxel retreatment is not reported, so all data from the 'One Prior Chemotherapy' group are used in the base case analysis.

The population presented as the base case, better reflects the UK population where it is estimated that only a minority (20%) of men with mCRPC receive a further chemotherapy after initial docetaxel treatment[3] see section 2.4 for a summary of the current treatment pathway. Furthermore, clinical opinion suggests that with the introduction of abiraterone acetate, the majority of patients would not be exposed to another line of chemotherapy (docetaxel re-treatment or mitoxantrone) before treatment initiation.[3] This 'One Prior Chemotherapy' population is therefore reflective of the population who would be eligible to receive abiraterone acetate in the UK.

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[j] 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.

[k] 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.

Key demographics of 'One Prior Chemotherapy' population compared to the ITT population are presented in Table 25. The 'One Prior Chemotherapy' group represents a population of 832 subjects, comprising 70% of the total population of the clinical trial. The ITT and 'One Prior Chemotherapy' groups were very similar in terms of demographic characteristics. Mean baseline PSA was slightly lower in the 'One Prior Chemotherapy' population compared to the ITT population, which may be expected in a population with fewer chemotherapy treatments. Economic evaluation using the ITT population from the COU-AA-301 study is presented as a scenario analysis.

Table 25 Characteristics of participants in the RCTs across randomised groups ('One Prior Chemotherapy' compared with ITT)

	[redacted]	[redacted]	xxx	
			AAP	**PP**
			(n=797)	**(n=398)**
Age: mean (SD)			69.1 (8.40)	68.9 (8.61)
Gender: mean (SD)			100	100
Race: %				
White			93.3	92.7
Black			3.5	3.8
Asian			1.4	2.3
American Indian/ Alaskan			0.4	0.0
Other			1.4	1.3
Weight (kg): mean (SD)				
Body surface area (m^2): mean (SD)				
Time since initial diagnosis (days): Mean (SD)			2610.9 (1630.21)	2510.0 (1712.36)
PSA at initial diagnosis (ng/mL): Mean (SD)			207.60 (835.658)	255.72 (855.441)
TNM stage at initial diagnosis: %				
Stage I			0	0
Stage II			12.9	13.1
Stage III			14.1	12.3
Stage IV			37.3	40.2
Incomplete reporting			35.8	34.4
Gleeson score at initial diagnosis: %				
<7			14.9	10.6
3+4=7			20.1	17.4
4+3=7			13.9	18.0
≥8			51.1	54.0
Evidence of disease progression (%):				
PSA only			29.9	31.4
Radiographic progression +/- PSA progression			70.1	68.6
Extent of disease: %				
Bone			89.2	90.4
Node			45.5	41.5
Liver			11.3	7.6
Lungs			13.0	11.4
Prostate mass			7.5	5.8
Other viscera			5.8	5.3
Other tissue			5.0	5.1
ECOG performance status: %				
0 or 1			89.7	88.7
2			10.3	11.3
Pain present: %			44.8	45.0
Baseline PSA (ng/mL): Mean (SD)			439.2 (888.48)	400.6 (810.55)

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

Model structure

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

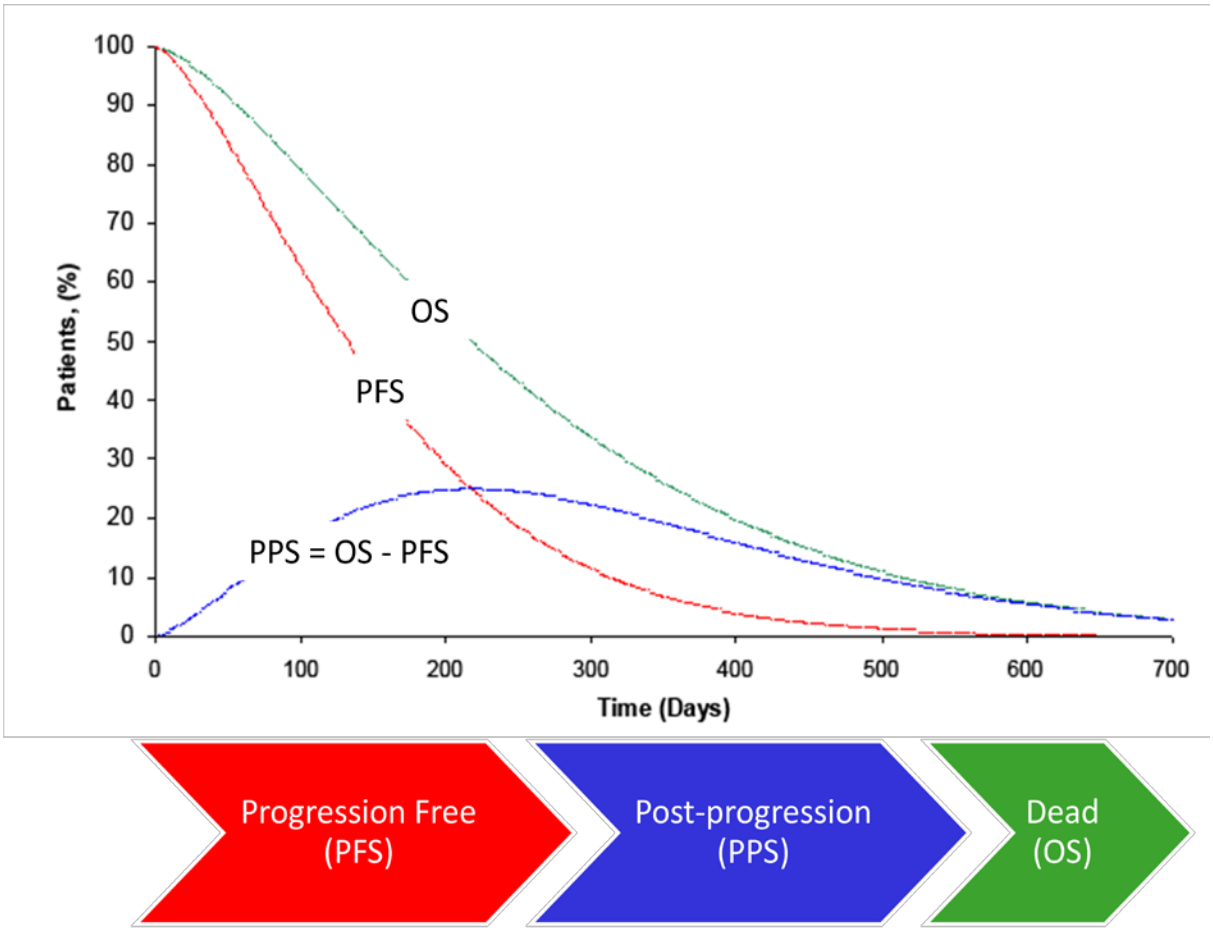

Figure 15. Schematic of the three health states used in the mCRPC economic model

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

A survival based decision analysis model incorporating the three health states shown in Figure 15 (PFS, PPS and OS) was developed in Microsoft Excel. A survival-based simulation model was chosen for several reasons. Firstly, it enables transparent representation of the health states relevant to mCRPC and simulates the transition from progression free to progressive disease in a clear, simple manner. Secondly, it relies on the observed PFS and OS data rather than on an assumed relationship between the PFS surrogate and the final outcome, OS. Thirdly, it is a commonly used approach in oncology,[83, 84] where PFS and OS are common endpoints and disease processes and treatments occur repeatedly over fixed time intervals until the occurrence of a terminal outcome. Finally, key cost effectiveness analyses (CEA) and cost utility analyses (CUA)

outcomes such as costs, life years, and QALYs are readily assigned to pre- and post-progression health states. Unlike a Markov model, transition probabilities are not explicitly calculated and used in the model. Instead, the number of patients remaining in each health state at each model cycle is calculated directly from the OS and PFS curves from the clinical trial for each comparator and additional assumptions are only made to model the final portion of the survival curve until all patients have died.

Current NICE guidelines do not recommend any specific treatment options for the mCRPC population following 1st line docetaxel treatment. Therefore, the model compares AAP with the current treatment option used in clinical practice, placebo + prednisolone (PP), and to the other comparator specified in the scope, mitoxantrone + prednisolone (MP). Clinical experts suggest that the PP comparator in the COU-AA-301 study is a fair representation of BSC in the England and Wales, as subjects in both arms were permitted to continue previously prescribed LHRH agonists and bisphosphonates and were also permitted to receive additional palliative radiation and acute glucocorticoids in addition to their prednisolone and/or abiraterone acetate. The main comparator for the model is PP, as clinical opinion suggests this represents current UK practice for the vast majority of patients. In the UK, only approximately 20% of mCRPC patients would be expected to receive a 2nd line chemotherapy treatment such as MP.

Patients enter the model having already received treatment involving docetaxel chemotherapy. The treatment discontinuation curves from COU-301-AA have been used to define the progression free state (PFS), an assumption which is discussed in detail in section 5.3.2.2. The post progression state (PPS) is defined by all patients surviving (OS) less those who remain progression free (PFS). Overall survival (OS) curves are used to direct patient flow into the dead state. The dead state is defined as the total number of patients minus those that have died. Costs and health effects (i.e. utility values) are assigned to each health state.

PFS = patients still on treatment

PPS = OS - PFS

Dead state = (1-OS)

People begin the model in the progression free state whereby they receive one of the treatment options (AAP, PP or MP). People who experience disease progression and do not die will transit to the progressive disease health state where treatment is stopped. At the end of each three week model cycle, patients may remain in the same health state or progress, but it is not possible to return to a pre-progression health state following progression.

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

PFS is an important endpoint in oncology trials, as time to progression has been shown to be a predictor of OS, and because the progression-free period, while on a cancer treatment, may be associated with better health-related quality of life than the post progression period. Therefore it is important to differentiate between the PFS and the PPS states within this model to capture potential benefits of being progression free.

The PFS period is divided into on treatment and off treatment periods, to allow estimation of costs and application of adverse event related disutilities. For AAP, during the whole PFS period subjects are assumed to be on treatment, consistent with the ‘treat to

progression' dosing of AAP and use of treatment discontinuation to define PFS. For MP, which has a defined maximum treatment duration, the median and maximum treatment duration is used to estimate a treatment discontinuation curve and assumes a constant hazard of treatment discontinuation truncated at the maximum duration.

The transition of patients from the PFS to the PPS is determined by treatment discontinuation from the COU-AA-301 for AAP and PP. Consistent with AAP being a medicine that is continued until disease progression, the PFS and treatment discontinuation curves are identical for AAP. Treatment discontinuation and transition into the PPS not only defines drug and administration costs for AAP and PP, but incremental differences in on-treatment follow-up costs, medical resource utilisation, AEs, and utility also drive both cost and effectiveness and serve to differentiate comparators. For MP, PFS is assumed to be the same as PP in the base case (section 6.3.1); scenario analyses explore the impact of assigning a longer duration of PFS to MP versus PP. Prednisolone administration is assumed to continue until death for all comparators including PP arm, as the use of corticosteroids is encouraged for palliative reasons in clinical trials even after active treatment ends. As MP is a fixed maximum duration treatment, PFS and treatment duration were modelled separately for this comparator. In the base case, a median treatment duration of 4 cycles and a maximum of 10 cycles[12, 29] is modelled for MP.

Table 26. Treatment duration for each comparator used in the model.

	Median Duration (in weeks)	Maximum Permitted Treatment Duration (in weeks)
AAP	N/A*	Until Progression
PP	N/A*	Until Death
MP	12	30

* Abiraterone treatment discontinuation is defined directly by respective Kaplan Meier data in the COU-AA-301 trial. As it is given until death, prednisolone treatment discontinuation will match OS.

Further details of how the COU-AA-301 trial data on treatment discontinuation has been used as a proxy for disease progression is described in Section 6.3.1.

6.2.5 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 two key outcomes that are central to the clinical treatment pathway for metastatic prostate cancer: disease progression and OS. Other key aspects captured in the model are grade 3/4 AEs, and quality of life associated with each health state. Patient benefits experienced on AAP compared to PP with respect to pain and fatigue are indirectly captured as part of the on treatment utility gain realised in the COU-AA-301 study.

6.2.6 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 27 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	This time horizon is assumed to be sufficient to capture the remaining lifetime of a mCRPC patient, as median survival in Phase III clinical trials for both abiraterone acetate and cabazitaxel did not exceed 15.1 months.	De Bono et al (2011)[13]
Cycle length	3 week cycle	This cycle reflects the dosing cycle of MP, as both AAP and PP are given daily and can be more readily adapted to any model cycle.	De Bono et al (2010)[12]
Half-cycle correction	Yes	A half cycle correction is used to adjust the proportion of patients in each health state.	
Were health effects measured in QALYs; if not, what was used?	Yes, FACT-P results from the COU-AA-301 study have been mapped to EQ-5D	Quality of life endpoints (FACT-P) was measured within the COU-AA-301 trial, and was deemed to be the most appropriate source. No other literature-based study populations matched that of the COU-AA-301 trial. A detailed description of the mapping methods used to calculate utility values is provided in Section 6.4.4.	Patient reported outcomes report from COU-301-AA[85]
Discount of 3.5% for utilities and costs	Yes	The discount rate applied to both costs and outcomes in the reference case was 3.5% per year per the NICE methods guide	Guide to the methods of technology appraisal (2008)[86]
Perspective (NHS/PSS)	NHS	The model takes the perspective of the NHS England and Wales.	
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 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 the three interventions used in the model (AAP, PP and MP) are all implemented in the model according to each of the summary of product characteristics (SPC) and as per the Marketing Authorisation and therefore are directly relevant to the comparators listed in the decision problem.

6.2.8 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.

There are no treatment continuation rules specified in the SPC. However, in the COU-AA-301 study treatment was stopped at disease progression as determined by individual investigators and this definition has also been applied to the economic model. UK expert clinical opinion also suggested AAP would be stopped at disease progression.

6.3 Clinical parameters and variables

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

For the comparison of AAP vs. PP, data from the 'Updated' analysis time point from the clinical trial COU-AA-301 were directly used in the model (median 20.2 months follow-up).[42]The 'Updated' analysis was favoured for use in the economic evaluation over the published 'Primary' analysis[11] as a larger proportion of events was captured in the 'Updated' analysis, introducing greater certainty around the clinical endpoints used in the model; OS and PFS. In addition, data for the 'One Prior Chemotherapy' population from the COU-AA-301 study was used in preference of the ITT data, as the 'One Prior Chemotherapy' population was felt to be more representative of the population that would receive abiraterone acetate in UK clinical practice.

Some data extrapolation was required to ensure the model captured all patients until they had entered the terminal death state. As extrapolations can be sensitive to the final portion of the curve, the shape of which is influenced by the censoring, the actual survival curves were truncated at a point where a reasonable proportion of patients were still contributing data and these data were robust (10% for OS, 5% for PFS). For the AAP vs. MP comparison, a lack of data necessitated several assumptions regarding OS and PFS as described below.

Overall survival

OS was modelled using Kaplan-Meier survival data directly from the COU-AA-301 trial. OS inputs for AAP and PP were therefore obtained directly from analyses of COU-AA-301 data. In order to conduct the cost-effectiveness analysis comparing AAP to MP as defined in the decision problem, it was assumed that OS for MP is equivalent PP. As the systematic review revealed a lack of both direct and indirect evidence to link these

comparators of interest in the post-chemotherapy patient population, outlined in Section 5.7.3, an assumption on OS for MP was required. For the NICE docetaxel HTA, the Assessment Group performed a meta-analysis of the results from three RCTs comparing MP with corticosteroids in chemotherapy naive populations. The pooled estimate of the HR for OS for mitoxantrone plus corticosteroid versus corticosteroid was 0.99 (95% CI 0.82 to 1.20).[30] As mitoxantrone has failed to demonstrate an OS benefit over corticosteroids in three chemotherapy naive studies; an appropriate assumption is therefore that MP is unlikely to have an OS benefit the post-chemotherapy setting. The assumptions for MP regarding OS, PFS and palliative benefits are explored in the economic model. Both OS and PFS data was extrapolated beyond the trial period, which is explained in detail in section 6.3.7. As discussed previously, curves were truncated where 10% of patients remained at risk to avoid undue influence of a small number of events under heavy censoring at the end of the curve.

Progression free survival

PFS is a common endpoint in oncology trials, however, the clinical definition of progression varies across trials and different tumour types. Within the COU-AA-301 study, there were two pre-defined PFS measures, modified PFS and radiographic PFS. Neither of these outcomes was determined to be an appropriate proxy for disease progression for modelling purposes for the following reasons:

- Modified and radiographic PFS were only measured at 3-month intervals at scheduled visits during the trial, whilst treatment discontinuation was a continuous variable that was recorded in the study case record forms.

- Neither of the pre-defined PFS endpoints (see section 5.5.3.2) used in the trial accurately reflect how disease progression (and hence treatment discontinuation) would be defined in UK clinical practice, as, unlike the trial definitions, clinical opinion suggests this decision would not be made based on a single measure of disease progression.

In addition to these two PFS outcomes, the protocol did specify a multi-factorial definition of when patients should discontinue treatment due to disease progression, which required three criteria be met:

- 1. PSA progression, and

- 2. Radiographic progression, and

- 3. Pain progression, SRE, increase in glucocorticoid use, or initiation of a new systemic anti-cancer therapy.

COU-AA-301 investigators have communicated that many patients discontinued treatment prior to meeting all three progression criteria; because of the advanced nature of disease in this patient population it was unreasonable and impractical to enforce that a subject undergo confirmatory PSA or radiological assessments, when they had clearly clinically progressed. Similarly, in UK clinical practice, the disease progression decision is not made based on such strict criteria. For this reason, the manner in which subjects actually discontinued treatment in the COU-AA-301 study is aligned with how disease progression and treatment discontinuation for patients on AAP would likely be determined in UK clinical

practice. The chosen definition of PFS (treatment discontinuation) relates directly to the treatment duration as well as the physician judgement of continuing benefit and therefore most closely reflects the quality of life changes and costs for this population. Treatment discontinuation as observed in the COU-AA-301 study is therefore the most accurate and composite measure of disease progression from an economic perspective. From this point on, this endpoint (time to treatment discontinuation or death) will be referred to and used to describe the period of PFS.

As stated previously, there is currently no comparative evidence available to estimate the relative efficacy (OS or PFS) of MP compared to AAP and PP within the post-chemotherapy population. However, there is some evidence (in chemotherapy naive populations) that MP may have a palliative benefit vs. corticosteroids alone with respect to pain and PFS.[45, 57, 58] Given the lack of RCT evidence coupled with the fact that MP is likely to have diminished benefit when used second line, the base case assumed that MP would have no PFS benefit over PP, but may confer some benefit with respect to pain whilst the patient is progression free (an equivalent utility benefit to that of abiraterone). Scenario analyses explore the impact of PFS for MP being improved compared to PP.

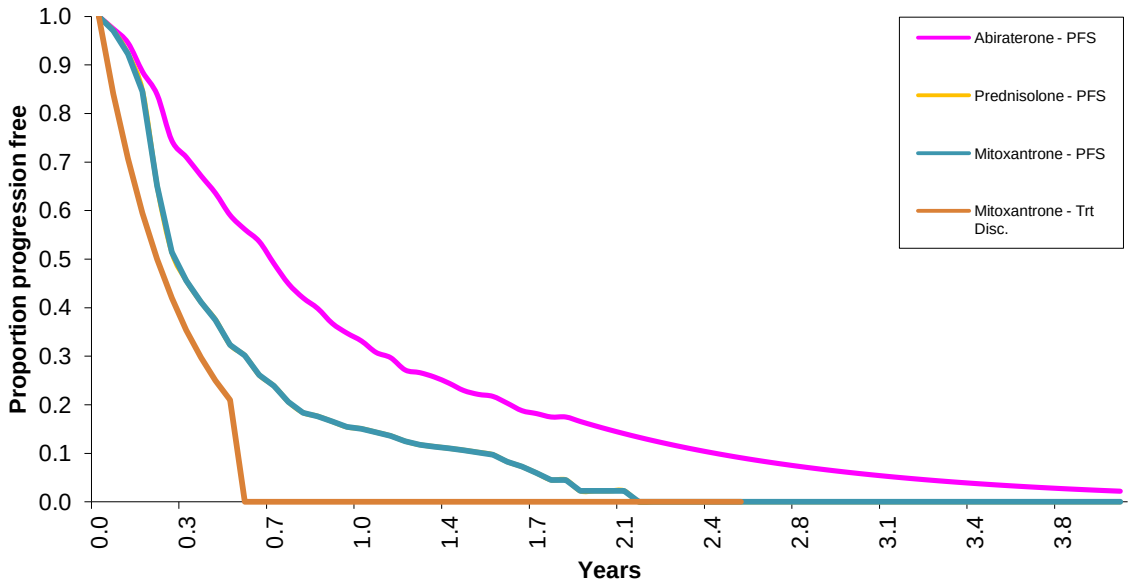

Figure 16. Progression free survival curves used in the economic model for each comparator (including extrapolation described in Section 6.3.7). Note that in the base case PFS for MP is assumed to be equal to PP.

Grade 3/4 adverse events

It is assumed that any incremental differences in AE rates between comparators would occur only when patients were actively receiving treatment, as defined by the treatment discontinuation curve. For the AAP vs. PP comparison Grade 3/4 events occurring in COU-AA-301 were analysed. The percentage of patients experiencing Grade 3/4 AEs in the two treatment arms was similar (60.4% in the AAP arm vs. 60.9% in the PP arm). Among the most frequently reported Grade 3 or 4 adverse events, the proportion of subjects affected in both groups was highly comparable. As there were no differences in

the incidence of these AEs between the two arms, individual AE costs and utilities were not directly incorporated in the model for this comparison. A separate analysis did uncover an incremental utility benefit for AAP over PP whilst on treatment (Section 6.4.3), so the model does inherently capture the balance of treatment benefit and side-effects each group experienced. Similarly, the event based MRU analysis captures (Section 6.5.6) differential AE costs and progression events for the two arms of the COU-AA-301 study.

For the AAP vs. MP comparison, Grade 3/4 AEs observed in the COU-AA-301 were indirectly compared to those observed in the MP arm of the TROPIC study.[12] Only adverse events that occurred at varying rates were considered (15 were identified), as incremental differences between treatments are the specific focus of economic analyses and drive results. Incremental differences (positive or negative) in event rates versus abiraterone were calculated by subtracting the raw AE rate of abiraterone from that of comparator for each specific AE. These incremental Grade 3/4 AE rates were assigned costs and disutilities to capture differences between treatments in terms of cost and patient health-related quality of life. The table below summarises the AEs incorporated in the model.

Table 28. Grade 3/4 AE rates considered in the model. AAP and PP AE rates are used from the COU-AA-301 study[42] ('Updated' ITT analysis) and the MP AE rates are taken from the TROPIC study.[12]

	AAP	PP	MP	
	Rate	Rate	Rate	*Difference from Abiraterone*
Neuropathy	[redacted]	[redacted]	1.1%	[redacted]
Neutropaenia	[redacted]	[redacted]	58.0%	[redacted]
Febrile Neutropaenia	[redacted]	[redacted]	1.3%	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	1.6%	[redacted]
Anaemia	[redacted]	[redacted]	4.9%	[redacted]
Oedema	[redacted]	[redacted]	0.0%	[redacted]
Hypokalaemia	[redacted]	[redacted]	0.0%	[redacted]
Hypertension	[redacted]	[redacted]	0.0%	[redacted]
Arthralgia	[redacted]	[redacted]	1.1%	[redacted]
Asthenia	[redacted]	[redacted]	2.4%	[redacted]
Diarrhoea	[redacted]	[redacted]	0.3%	[redacted]
Dyspnoea	[redacted]	[redacted]	0.8%	[redacted]
Fatigue	[redacted]	[redacted]	3.0%	[redacted]
Nausea	[redacted]	[redacted]	0.3%	[redacted]
Vomiting	[redacted]	[redacted]	0.0%	[redacted]

6.3.2 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.

Unlike a Markov model, this survival based decision analysis model does not explicitly calculate transition probabilities, further detail are contained in Section 6.2.4.

6.3.3 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.

Not applicable

6.3.4 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?

Not applicable

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

- 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 speciality 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).

Patient level data on the treatment pathway for mCRPC patients post-docetaxel is limited in the UK. Therefore, clinical experts were consulted to obtain details relating to the current use of treatments in UK clinical practice as well as the medical resources used for the administration of these treatments and for treating AEs. The generation of this data involved the following steps:

- Qualitative phase (n=11) in depth interviews with oncologists were undertaken to obtain a detailed understanding of the key treatment options (and associated health care resources) for patients with mCRPC post-chemotherapy. This information was used to define the survey questions in the Quantitative phase.

- Quantitative phase (n=57) consisted of an online survey with oncologists (n=41), oncology nurse specialists (n=10) and hospital pharmacists (n=6) with the objective of providing estimates of:

[I] 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.

- Current 2nd line treatment options (and proportion of patients)
- Future treatment options (and proportion of patients)
- Dosing and treatment cycle duration for each treatment option (mitoxantrone, BSC and abiraterone acetate)
- Imaging diagnostic tests and clinical laboratory tests performed prior to, during following disease progression for each treatment option
- Treatment of AEs
- Healthcare professionals involved in the care of mCRPC patients for AEs related to these treatments
- The anticipated impact of AEs on patient quality of life.

The estimates generated in this process were taken forward for discussion with the consensus panel of experts

- Consensus panel (n=8) of five oncologists and three lead chemotherapy nurses discussed the findings of the quantitative survey with the objective of reaching a consensus on each of the key values. Following on from this consensus panel, a telephone conference with 5 of the clinical oncologists was conducted to resolve some outstanding queries which were not addressed at the consensus panel.

The Qualitative and Quantitative phases were conducted as market research under the British Healthcare Business Intelligence Association guidelines. The clinical experts did not declare any conflict of interest. At the consensus meeting, the panel were presented with the aggregated results of the quantitative survey to provide a foundation for discussion. This process involved individuals voicing their opinion on each value sequentially, then if there was discrepancy, a discussion followed. After discussion, the consensus panel were then asked to state their opinion. This process continued until 60% or more of the panel agreed.

Summary of selected values

6.3.6 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 29 Summary of variables applied in the economic model for the Base case analysis ('One Prior Chemotherapy' population)

Variable	Value	SE (distribution)	Reference to section in submission
Model settings			
Cycle length (wks)	3		Section 6.2.6
Time horizon (yrs)	10		Section 6.2.6
Discount rate for costs	0.035		Section 6.2.6
Discount rate for health	0.035		Section 6.2.6
Effectiveness			
OS – AAP	AAP arm OS Kaplan Meier Data from COU-AA-301		Section 6.3.1 / 5.5.3.1

OS AAP - extrapolation	Constant Hazard		Section 6.3.1 / 5.5.3.1
OS – PP and MP	PP arm OS Kaplan Meier Data from COU-AA-301		Section 6.3.1 / 5.5.3.1
OS PP and MP - extrapolation	Constant Hazard		Section 6.3.1 / 5.5.3.1
PFS – AAP	AAP arm PFS Kaplan Meier Data from COU-AA-301		Section 6.3.1 / 5.5.3.2
PFS AAP – extrapolation	Constant Hazard		
PFS – PP and MP	AAP arm PFS Kaplan Meier Data from COU-AA-301		
PFS PP and MP - extrapolation	None required		
Costs			
Comparator Drug Costs per model cycle			Section 6.5.5.
Abiraterone acetate	[redacted]		
Prednisolone	2		
Mitoxantrone	200		
Drug administration cost - Administration Visit Cost (Active Tx)			Section 6.5.5.
Abiraterone acetate	0.00		
Prednisolone	0.00		
Mitoxantrone	248.45	24.85	
Unplanned, Event Related Medical Resource Utilisation			Sections 6.5.6., 6.5.7.
AE management Cost (Progression Free)			Section 6.5.7
Abiraterone acetate	[redacted]	[redacted]	
Prednisolone	[redacted]	[redacted]	
Mitoxantrone	[redacted]	[redacted]	
AE management Cost (Post Progression)			Section 6.5.7
Abiraterone acetate	[redacted]	[redacted]	
Prednisolone	[redacted]	[redacted]	
Mitoxantrone	[redacted]	[redacted]	
Terminal (1-time cost)			Section 6.5.6
Abiraterone acetate	[redacted]	[redacted]	
Prednisolone	[redacted]	[redacted]	
Mitoxantrone	[redacted]	[redacted]	
G-CSF Cost			Section 6.5.6
G-CSF cost per cycle	686	68.64	
Scheduled, Disease Related Follow-up Costs (per month)			Section 6.5.6
Progression Free			
MP On Treatment,	[redacted]	[redacted]	
MP Off Treatment	[redacted]	[redacted]	
AAP first 3 months on treatment	[redacted]	[redacted]	
AAP Month 4 through end of treatment	[redacted]	[redacted]	
PP	[redacted]	[redacted]	
Post Progression			
All Treatments	[redacted]	[redacted]	
Utility inputs			
Progression Free Utility of mCRPC	[redacted]	[redacted]	Section 6.4.9.
Incremental utility benefit on treatment			Section 6.4.9.
Abiraterone	[redacted]	[redacted]	
Prednisolone	[redacted]		
Mitoxantrone	[redacted]	[redacted]	
Post-progression utility	0.500	0.080	Section 6.4.9.
Utility Decrement Per Grade 3/4 Adverse Event			Section 6.4.9.

Neuropathy	[redacted]	[redacted]	
Neutropaenia	[redacted]	[redacted]	
Febrile Neutropaenia	[redacted]	[redacted]	
Thrombocytopaenia	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	
Oedema	[redacted]	[redacted]	
Hypokalaemia	[redacted]	[redacted]	
Hypertension	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	
Asthenia	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	
Disutility Due to Grade 3/4 Adverse Events While On Treatment (Compared to AAP)			Section 6.4.9.
Prednisolone	[redacted]	[redacted]	
Mitoxantrone	[redacted]	[redacted]	

6.3.7 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.

Because a small proportion of patients were alive at the end of the follow-up period considered in the 'Updated' COU-AA-301 trial analysis, an approach to extrapolating survival data beyond the trial period was required to estimate survival, costs and health effects over a patients' lifetime. Estimates of the effect of AAP versus PP on OS within the COU-AA-301 trial were taken directly from the Kaplan-Meier plots. Hence, this estimate of OS allowed the OS benefit of AAP to change over time, as it does within the COU-AA-301 trial. As events were not observed for all patients in COU-AA-301, curves were extrapolated with reference to the rate of progression up till that point, in the base case the extrapolation assumed a constant hazard rate (exponential curve), as has been previously advocated.[84, 87] The choice of functional form for the extrapolation could not be unequivocally made based on tests of fit or from visual examination of the curves (Figure 17 to Figure 20), see appendix 17 for further detail. As recommended in NICE DSU technical support document 14[88] a single function was fitted for each treatment and as such the exponential curve appears a reasonable middle ground to optimise the fit; extrapolation using the Weibull function has been tested in sensitivity analyses. Data from other mCRPC studies[11, 12, 29, 56] support an assumption of a monotonically increasing hazard, such a Weibull function. Figure 17 to Figure 20 describe the OS curve fitting functions for both AAP and PP at both the early phase of the curves and across the entire curves. Due to the length of follow up and poor prognosis of patients at this stage of prostate cancer the extrapolation accounts for a relatively small proportion of the overall and incremental survival time.

The constant hazard extrapolation replaced the Kaplan-Meier data when only 10% of patients in each arm remained at risk, and continued to the end of the model time horizon.

This 10% cut-off of patients at risk was chosen because the Kaplan-Meier data had much censoring at the end of the trial period, making the Kaplan-Meier estimates at these points less reliable. The constant hazard rate was calculated using formula (1).

$$h(t_i) = 1 - \left(\frac{s(t_i)}{s(t_{i-1})} \right)^{\frac{1}{(t_i - t_{i-1})}} \qquad (1)$$

Here, the average hazard rate is calculated by the proportion of patients surviving at two time points (i.e., t_i and t_{i-1}) during the trial period. The two time points considered are the beginning of the trial and the point at which 10% of patients remain at risk

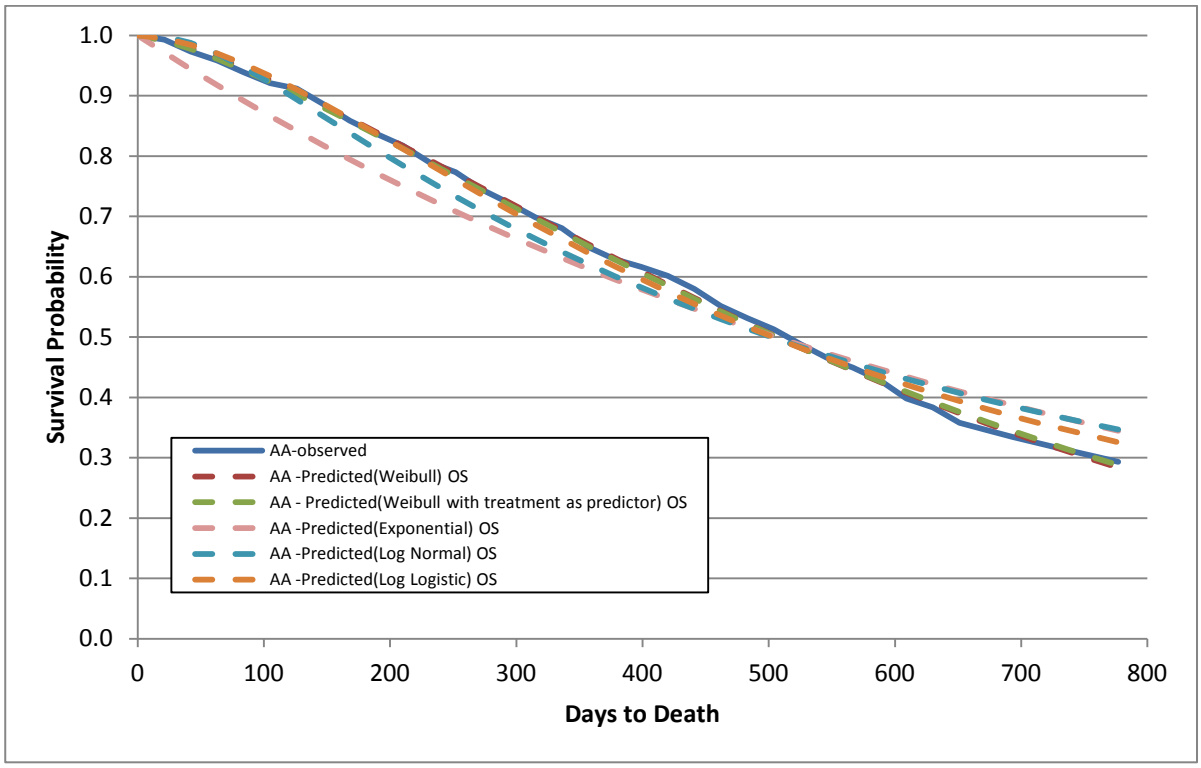

Figure 17 Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - AAP: 0-800 Days

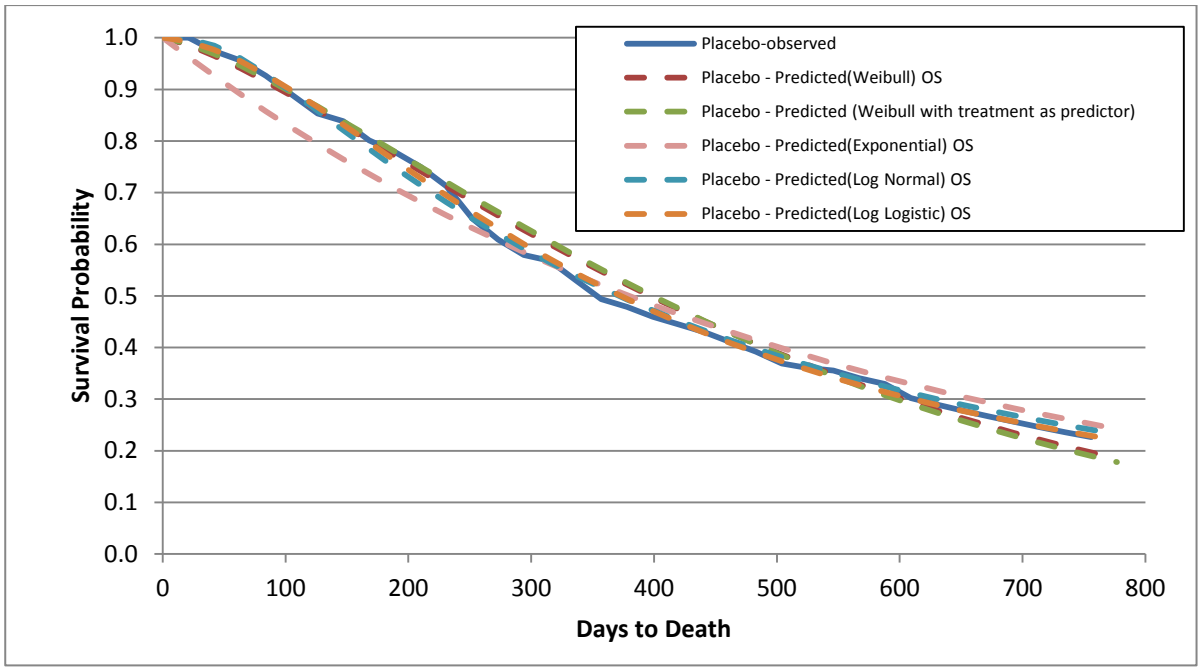

Figure 18 Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - PP: 0-800 Days

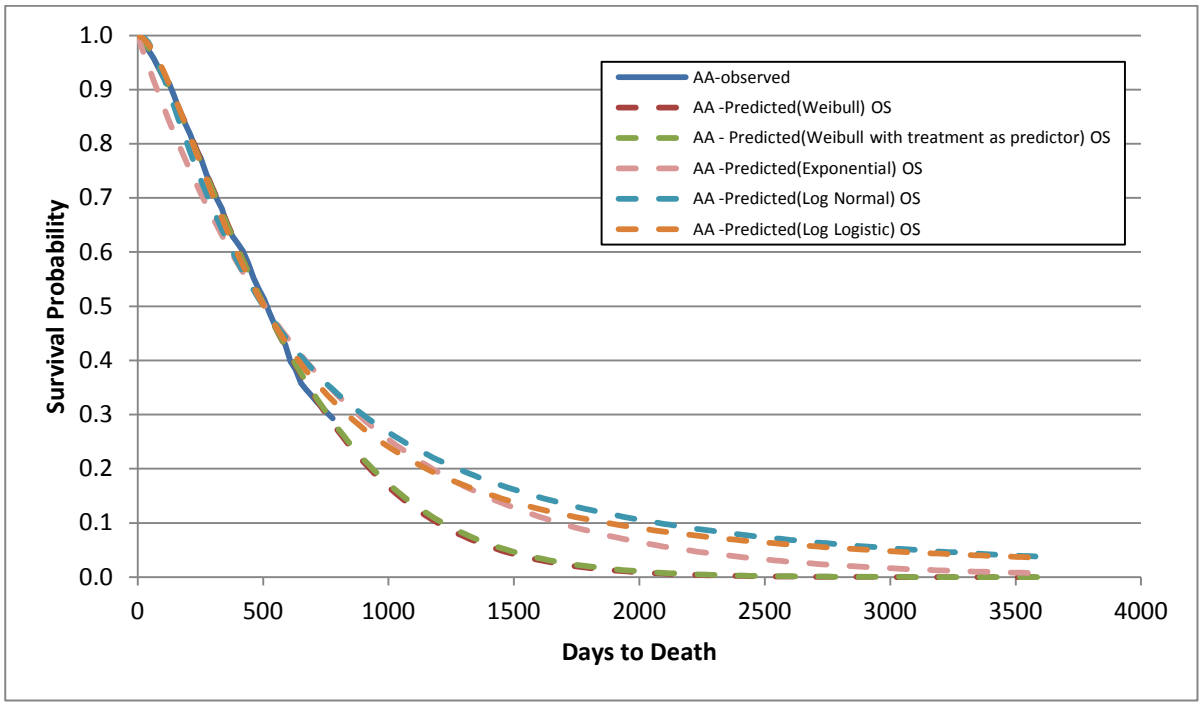

Figure 19. Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - AAP: 0-4,000 Days

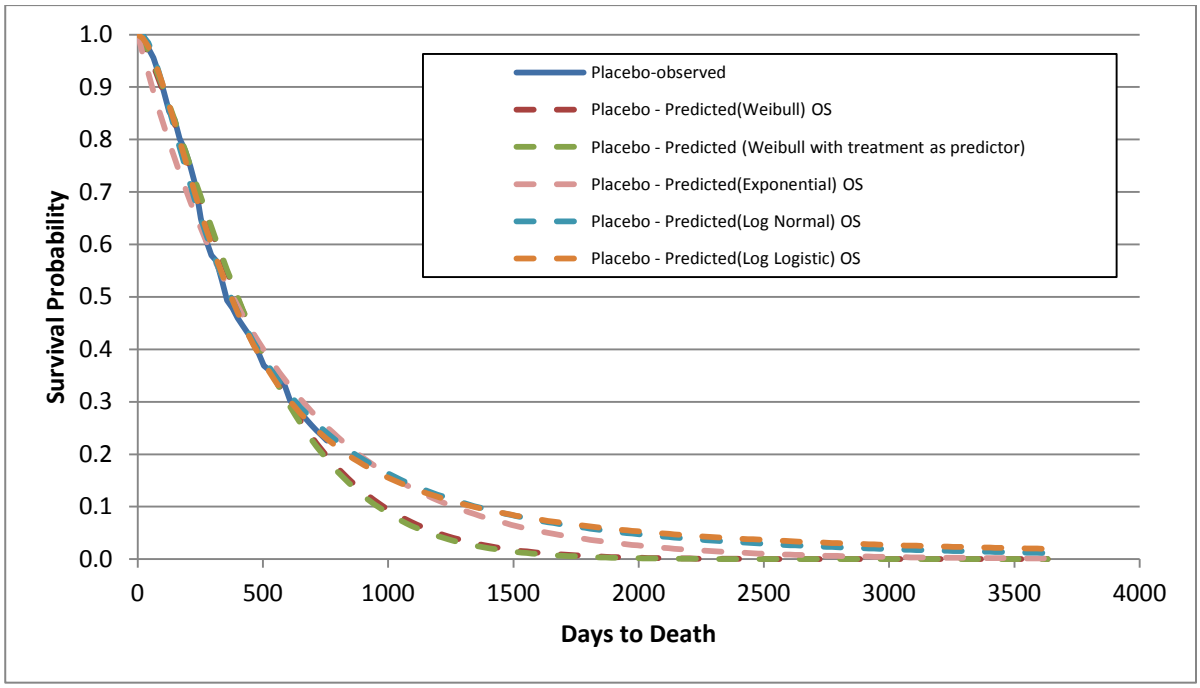

Figure 20 Parametric Curve Fits - Overall Survival – 'One Prior Chemotherapy' - PP: 0-4,000 Days

The same methods and assumptions were applied for PFS, however KM curves were truncated when 5% of patients remained at risk due to less censoring compared to the OS data. Extrapolation was not required for the PP arm for PFS, due to the number of progression events observed in the 'Updated' analysis. A constant hazard for PFS extrapolation was used in the base case and sensitivity analysis explored extrapolation using a Weibull function on the AAP curve, further details in Appendix 17.

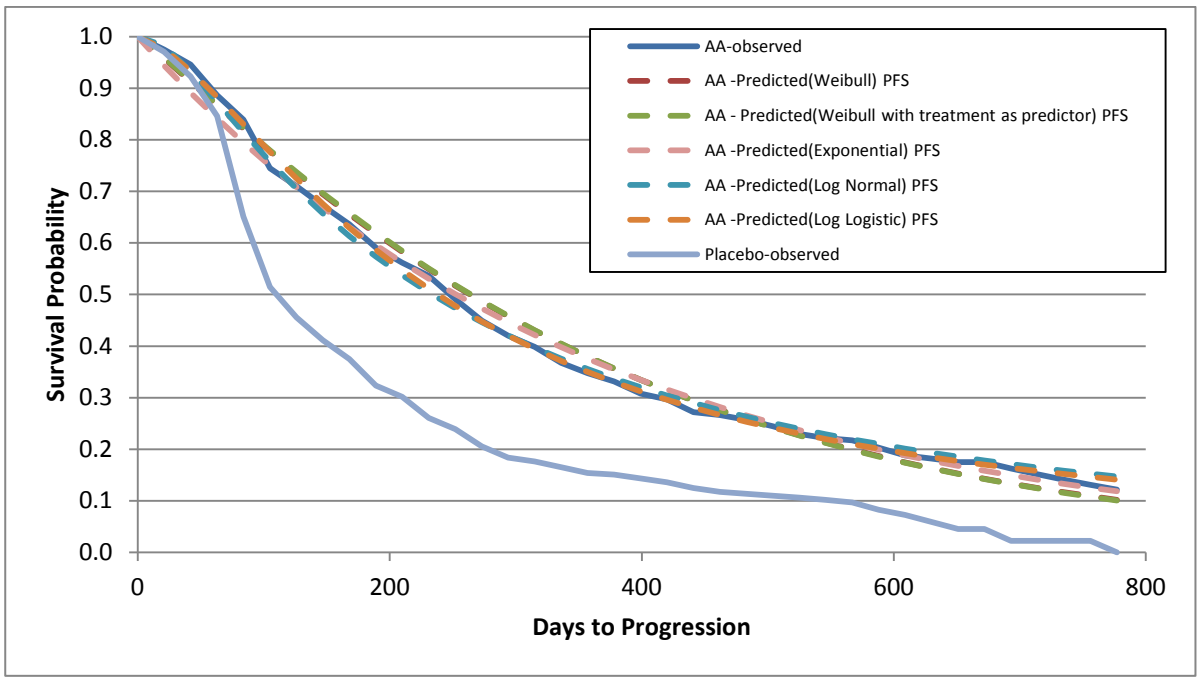

Figure 21 Parametric Curve Fits - PFS – 'One Prior Chemotherapy': 0-800 Days.

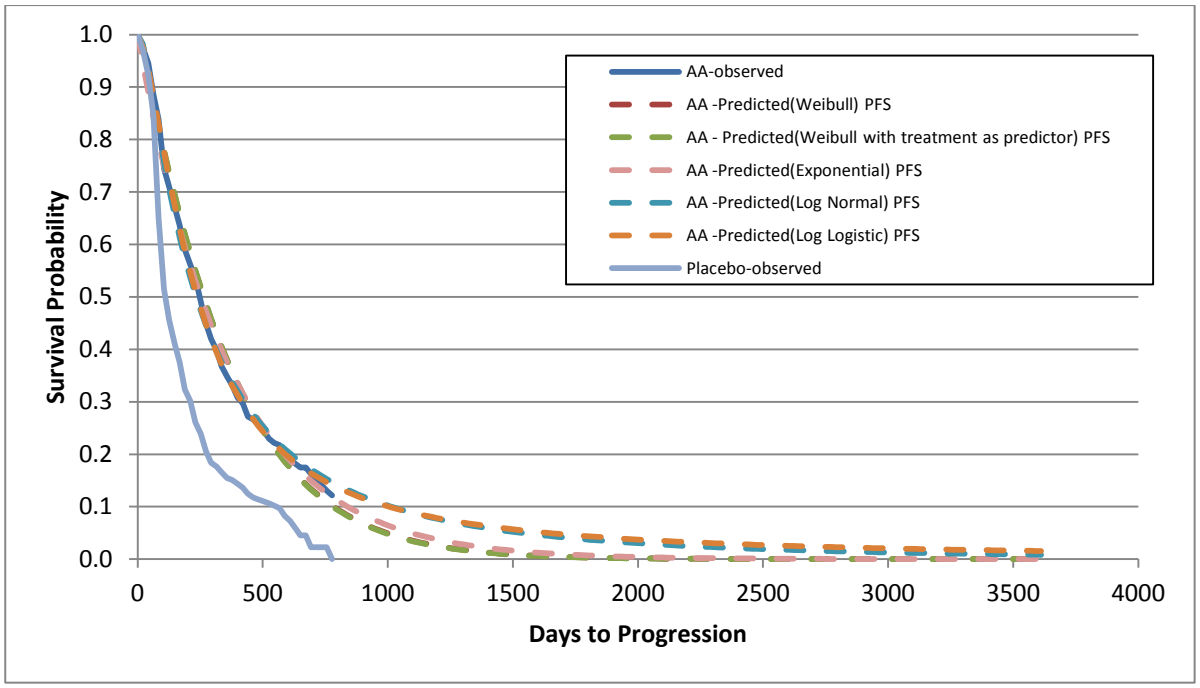

Figure 22 Parametric Curve Fits - PFS - 'One Prior Chemotherapy': 0-4,000 Days.

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

Assumptions made regarding the model clinical inputs include:

Assumption	Rationale
COU-AA-301 is the most appropriate study to generate clinical outcomes, utility values and medical resource costs for which to model the cost-effectiveness of AAP compared to PP and MP for the mCRPC population in the UK.	Individual patient level data from a large number of subjects within the COU-AA-301 study was used to generate OS, PFS, progression free survival utility values, disutility associated with AEs and utility benefit associated with treatment, as well as during treatment MRU.
AAP is administered until disease progression	In COU-AA-301, AAP was only administered until disease progression, as is expected in UK clinical practice.
'One Prior Chemotherapy' population is more reflective of the population expected to receive AAP in the UK than the ITT population	UK mCRPC patients receive fewer lines and types of chemotherapy compared to those subjects in the mutli-country COU-AA-301 study. Clinical opinion also suggests that once AAP is available patients will be very unlikely to receive more than one line of prior-chemotherapy (e.g. docetaxel) as subsequently chemotherapies are not recommended by NICE guidelines/guidance.
OS for MP and PP is assumed to be equivalent	There is no clinical evidence supporting an OS advantage over corticosteroid monotherapy in any line of therapy for mCRPC patients.
Treatment discontinuation data from COU-AA-301 for AAP and PP are and appropriate proxy for PFS	In the COU-AA-301 study, subjects discontinued treatment at the point of disease progression. Other PFS outcomes used in the COU-AA-301 study (rPFS and mPFS) were not necessarily associated with treatment discontinuation, as investigators did not define a subject as having progressing disease based on a single clinical assessment measure. This is expected to align with UK clinical practice.
PFS for MP and PP is assumed to be equivalent	There is no clinical evidence supporting a PFS advantage over corticosteroid monotherapy in post-docetaxel mCRPC populations.
Treatment discontinuation for MP is defined by an exponential function	The median treatment duration reported in the TROPIC study was used to define treatment discontinuation for MP
Extrapolation of the OS and PFS curves assumes a constant hazard rate	Curves were extrapolated with reference to the rate of progression up till that point and assumed a constant hazard rate (exponential curve) as has been previously advocated in other HTA appraisals.
Incremental differences in the risk of Grade 3/4 AEs between AAP and MP treatment are limited to the time in which patients are receiving active treatment.	The risk of adverse events was assumed to not exist once treatment with AAP or MP had been discontinued.
Post-progression utility values were assumed to be 0.50 for all treatment arms	A systematic review of the literature identified that the post-progression utility estimates from in the Sandblom et al., study (2004) were the most appropriate to use in the model.

6.4 Measurement and valuation of health effects

Patient experience

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

Research in patients with prostate cancer shows that HRQL declines significantly as the disease progresses. Men with early prostate cancer have been found to experience decreasing vitality and increasing psychological distress over the 12 months following diagnosis,[89] and psychological function can be impaired.[90] Patients with PC have also been reported to suffer from fatigue, sexual disturbances, and interruption of social relationships.[8] Once prostate cancer progresses to the metastatic stage, patients complain of general fatigue, cancer pain, restriction of daily life, and urinary disturbance.[9] The most significant morbidity in mCRPC is bone metastasis, and the presence of SREs is significantly associated with poorer HRQL.[10] SREs, such as pathologic fractures and spinal cord compression, are major causes of morbidity in patients with prostate cancer and can lead to other comorbidities including pain.[91, 92]

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

Studies demonstrate that HRQL of patients with mCRPC declines considerably in the last months before death,[93] and the scores from patients with metastatic disease are lower in terms of functioning, physical and social domains, compared to patients with localised disease.[94] Patients with mCRPC suffer from disease symptoms and can also be impacted by the side effects of treatments. Symptoms such as nausea, vomiting, dyspnoea or appetite loss, and pain have been observed to worsen with time.[93, 95] Of all factors affecting health-related quality of life, however, pain is usually considered the most prominent factor for patients at this stage of their disease.[96] Pain control is therefore considered to be paramount to improve symptom burden and thus HRQL in mCRPC patients.[9] As a further decline in HRQL of mCRPC patients is associated with progression, delaying this will have substantial benefits to patient quality of life. In progressing disease, patients are likely to experience more pain due to bone metastases and hence more likely to experience SREs. In the progressing phase, and when no further active anti-cancer treatments are being considered, the focus shifts to palliative care to slow and reduce the further decline of patient quality of life. Adequate pain and symptom management, avoidance of inappropriate prolongation of the dying process, achievement of a sense of control, and the strengthening of relations with loved ones have been found to be the most important domains from the patient's perspective of palliative treatment.[97]

Quality of life in mCRPC patients has been assessed in several studies, and utilities elicited from men suffering from the disease, their partners, clinicians and also by the general population using different methods, Table 32.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (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 in the COU-AA-301 trial was measured using the FACT-P questionnaire. The FACT-P was evaluated at day 1, and at cycles 4, 7, 10 and then every 6 cycles thereafter and at treatment discontinuation. Pain (BPI-SF) and fatigue (BFI) were also evaluated at Screening, Day 1, Day 15, Cycles 2-10 and at treatment discontinuation. The FACT-P assessment is comprised of the Functional Assessment of Cancer Therapy – General (FACT-G) and a prostate cancer subscale. The FACT-G consists of five subscales measuring physical, functional, social/family, and emotional well-being in addition to satisfaction with the doctor-patient relationship.[98] The prostate cancer subscale of the FACT-P includes 12 items specifically designed to measure the health related quality of life in patients with prostate cancer.[99] FACT-P has been widely used in prostate cancer studies and is a well-validated and clinically meaningful assessment of disease burden. FACT-P does not permit calculation of preference based health status (utility) values, therefore FACT-P data from the COU-AA-301 study was mapped to EQ-5D using the methodology outlined in section 6.4.4. Mapping enabled utility values for the pre-progression health state, the impact of AEs and an on-treatment utility benefit to be estimated from the COU-AA-301 data.

Using the mapping transformation outlined in the section 6.4.4, FACT-P data collected whilst subjects were on treatment in the COU-AA-301 study for the ITT and the 'One Prior Chemotherapy' population was mapped to EQ-5D. Using repeated measures analysis, the mean utility of all on-treatment values, representing the pre-progression health state, was estimated to be [redacted] This analysis also highlighted a utility benefit in the pre-progression health state for AAP subjects compared to PP subjects ([redacted]). This utility benefit was statistically significant and biologically plausible, and captures the average pain, fatigue and functional status improvements that AAP subjects experienced during the study. It should be noted this benefit is inclusive of any disutility associated with AEs and therefore no additional consideration of adverse events is required for comparisons of AA vs. PP. This treatment benefit is also assigned to MP until disease progression in the model.

Using the same utility mapping algorithm, utility of patients experiencing a Grade 3/4 AE was calculated relative to those that did not experience such an event. This analysis established that the occurrence of at least one Grade 3/4 AEs during the treatment period was, on average, associated with a [redacted] decrease in utility though this difference was not statistically significant. In contrast, a review of the solid tumour literature determined that disutility values for specific AEs varied but also varied within an AE between different studies e.g. febrile neutropaenia ranged from [redacted] to [redacted], see Table 33. In addition, some AEs were not located in the search, including thrombocytopaenia, hypokalaemia and oedema. As the data in the published literature was heterogeneous and not specific to Grade 3/4 AEs and the majority of adverse events were more frequent for MP than AAP,

the uniform disutility of [redacted] used in the model for all Grade 3/4 AEs offers a conservative yet relevant approach. Therefore, based on the incremental differences in Grade 3/4 AE rates between MP and AAP, and the disutility of each AE, the model calculates a composite disutility of [redacted], which was applied to the on-treatment utility of MP. No additional impact on utility due to the general malaise and fatigue that patients on chemotherapy frequently suffer was included in the modelling.

Mapping

6.4.4 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.

The quality of life measure captured in COU-AA-301 (FACT-P) was selected as the assessment's content and psychometric properties have been well validated,[99] and clinically meaningful changes in the FACT-P have been determined.[100] EQ-5D was not assessed in COU-AA-301, therefore it was necessary to use an algorithm to map FACT-P from the COU-AA-301 to EQ-5D scores. A review of the literature identified a mapping study by Wu et al., (2007).[101] A discrepancy was identified in the algorithm within the Wu (2007) publication (see Appendix 15 for further details), an algorithm was generated using an alternative UK relevant data source, subsequently referred to as the Adelphi dataset.

The Adelphi dataset contained both EQ-5D and FACT-P data captured from cross-sectional research study: the Disease Specific Programme (DSP) for Prostate Cancer.[102] This research collects data from five European countries (France, Germany, Italy, Spain and the UK) via physician interviews, physician workload questionnaires, patient record forms, and patient self-completion records. Data from a subset of patients in this DSP with mCRPC (n = 291) were analysed and an algorithm to map the FACT-P data to EQ-5D data was developed. The utilities calculated using this algorithm were based on a UK-specific EQ-5D value set.[103]

The Adelphi dataset mapping algorithm included the same predictive variables as those suggested by Wu et al., (2007). The best performing model for the UK population (considered in the economic model) was the OLS model. The best performing model for the UK population (considered in the economic model) was the OLS model. The 10-fold cross validation R^2 results for all four models were evaluated, and for the UK population the OLS model had a relative predictive validity of 0.385. Thus, the OLS model explains 38.5% of the observed EQ5D variation in the validation sample. Further explanation of the mapping algorithm generated using the Adelphi DSP is provided in Appendix 15 and will be presented as a podium presentation at the upcoming European meeting of the ISPOR.

HRQL studies

6.4.5 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 9.12, appendix 12.

A systematic review of the literature was conducted to identify all HRQL publications that may provide:

- HRQL information for the comparator relevant to the decision problem MP
- Utility values for the health states associated with this mCRPC

These research questions were explored by updating the systematic review undertaken by NICE for the docetaxel HTA review in 2006. Published literature databases were examined from 1st January 2005 (the year the TA 101 search was conducted) until 19th August 2011. The literature databases searched are listed in Table 30.

Table 30: Literature databases searched

Database	Platform
MEDLINE® (including MEDLINE® in-process, and other non-indexed citations)	Embase.com & PubMed
Embase®	Embase.com
Cochrane® (including Cochrane systematic reviews, other reviews, clinical trials, and economic evaluations)	The Cochrane® Library

The search strategies used in the TA 101 review were written for the Ovid search platform. These searches were translated from the Ovid format to the correct format for each of the search platforms listed in Table 1. The translated searches were validated by confirming that they returned the seven studies identified and included in the QoL review of the TA 101 assessment. The translated search strategies are presented in Appendix 9.12. Please note that the EconLit® database was searched via the AEAweb.org platform in a previous review of the health-related QoL of patients with advanced metastatic prostate cancer, with no studies meeting the inclusion criteria identified.

To be included in the review, studies had to meet pre-defined eligibility criteria which were specified in the protocol, see Appendix 9.12. In brief, studies were excluded if they were not primary studies, were not in a population, or contained a sub group, of subjects with advanced or metastaticdisease. To be included, studies also needed to report utilities or QoL specific measures.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded and imported in Excel for screening. Citations were first screened by two reviewers in parallel based on the title and abstract supplied with each citation. Those that did not match the eligibility criteria were excluded at this “first pass”. Any discrepancies between the two reviewers were checked and reconciled by a third reviewer. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded in the first pass. Full-text copies of all references that could potentially meet the eligibility criteria were ordered at this stage. In instances when it was not possible to include or exclude citations based on the title and abstract, full-text copies were ordered. The eligibility criteria were

applied to the full-text citations. This stage was also performed by two reviewers in parallel with a third reviewer reconciling any discrepancies.

The search strategy identified 423 citations; screening of these citations based on the information provided in their titles and abstracts excluded 374 citations (any copies and duplicates were also excluded at this stage). Full texts were obtained for the remaining 49 citations and they were screened based on the information provided in their full texts. The literature review identified 12 studies that assessed HRQL in a mCRPC patient population. A summary of the systematic review flow is described in Figure 23.

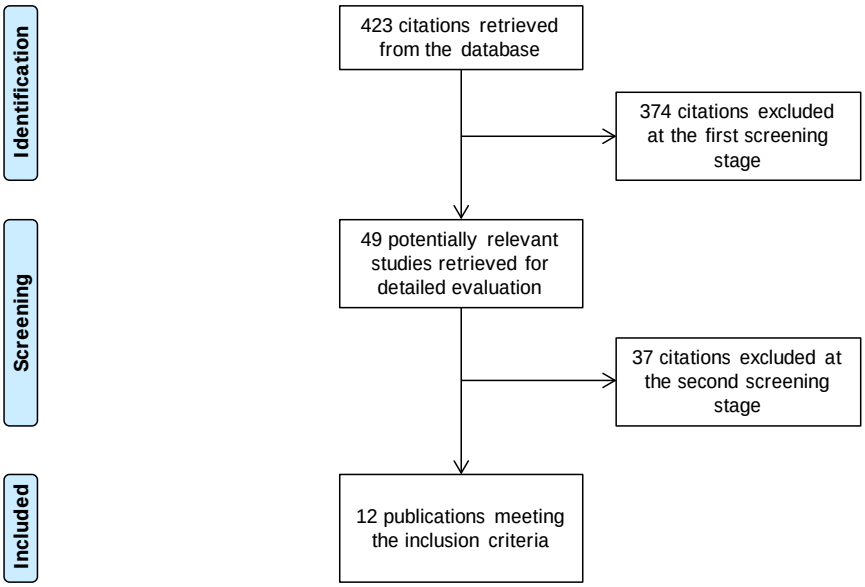

Figure 23. HRQL review inclusion flow.

This update of the original systematic review conducted for the Docetaxel HTA in 2006, identified one additional study that reported baseline EQ-5D in a population of mCRPC patients, (Sullivan et al., (2007)[93]). A further study was identified that captured change in EQ-5D from baseline (as well as change in other QoL assessments, however baseline EQ-5D was not reported in this study (Krahn et al., (2007)[104]). The review failed to identify any studies that explored quality of life associated with MP treatment. Of particular interest to the decision problem was the identification of one study that explored the mapping of FACT-P to EQ-5D (Wu et al., (2007)[101]) described in Section 6.4.4. The remaining studies reported various HRQL measures for this patient population. A summary of the measures reported in each of the 12 studies are captured in Table 31.

Table 31. Summary of QoL measures captured in 12 studies identified in the updated systematic review of the literature.

	EQ-5D	SF-36	HUI	PORPUS	QLQ-C30	FACT-P/ FACT-G	BSI	Other
Couper et al., (2010)[89]		X					X	Mini-MAC
Dawson et al., (2007)[105]					X	X		
DePuy et al., (2007)[10]						X		
Dacal et al., (2006)[106]		X						
Gore et al., (2005)[107]		X						UCLA PCI-SF, McCorkle and Young's Symptom Distress Scale, FACIT-Sp, PEPPI
Kato et al., (2007)[108]		X						UCLA-PCI
Krahn et al., (2007)[104]	X		X	X	X			PCI
Love et al., (2008)[90]		X						BSI, DAS, FRI, CIDI
Stewart et al., (2005)[109]								Utility data derived from standard gamble and time trade off.
Sullivan et al., (2007)[93]	X				X	X		
Ueda et al., (2006)[110]		X						10 point visual analog scale
Wu et al., (2007)[101]								Utility mapping study: FACT-P to EQ-5D

EQ-5D: EuroQoL Five Dimension, FACT-P: Functional Assessment of Cancer Therapy – Prostate, HUI: Health Utility Index, PORPUS: Patient-Oriented Prostate Utility Scale – indirect utility instrument, SF-36: Short Form 36, BSI: Brief Symptom Inventory. UCLA-PCI: University of California in Los Angeles Prostate Cancer Index, UCLA PCI-SF, Mini MAC: Mini-Mental Adjustment to Cancer scale, FACIT-Sp: Functional Assessment of Chronic Illness Therapy Scales Spirituality subscale

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

This update of the original NICE systematic review in HRQL only identified one additional study that provides utility values of potential use in the model, Sullivan et al., (2007).[93]. A summary of utility values identified in the literature is presented in Table 32. Patients provided lower utility values compared to physicians[111] and their partners[112], but the general population estimated lower values still.[113] It should be noted that clinical treatment pathway has changed from the time these studies were conducted, that is, these studies were conducted prior to the NICE recommendation of docetaxel in 2006. In summary, utility values in the literature range from 0.66-0.86 for localised disease, 0.53 to 0.92 for metastaticdisease and from 0.23-0.715 in mCRPC disease, see Table 32.

Table 32. Spectrum of health related quality of life utility values for prostate cancer, updated from NICE HTA review (cited from Collins et al., (2007)[72]). Note the only addition to the table was Sullivan et al., (2007).

	---------- SPECTRUM OF DISEASE SEVERITY ---------->									
Source	**Localised**			**Metastatic**			**mCRPC**			**Methodology**
Bennet (1997)[111]				0.92		0.83			0.42	TTO (Median), Physicians Opinion (N=47)
				0.88		0.53			0.05	Pts w/ Localised PC Opinion (N=27)
				0.78		0.58			0.05	Pts w/ Metastatic PC Opinion (N=17)
Chapman (1998)[114]		0.78			0.51				0.2	TTO (mean), Impersonal (N=31)
		0.78			0.72				0.35	TTO (mean), Personal (N=28)
Chapman (1999)[115]		0.84			0.66				0.23	TTO (mean), Patient opinion (N=57)
Krahn (2003)[113]		0.86				0.85				Patient PORPUS - SG Mean (N=141)
		0.8				0.75				Patient PORPUS - RS Mean (N=141)
		0.8				0.81				HUI-SG Mean
		0.66				0.62				QWB-RS Mean
Sandblom (2004)[95]			>16M				12-8M	8-4M	4-0M	
			0.77				0.58	0.54	0.46	EQ-5D (mean), Value
			0.70				0.57	0.53	0.45	EQ-5D (mean), VAS
Volk (2004)[112]					0.72		0.55			TTO (mean), Husbands (N=168)
					0.86		0.66			TTO (mean), Wives (N=168)
					0.83		0.62			TTO (mean), Couples (N=168)
Stewart (2005)[109]	0.84	0.81	0.71	0.67					0.25	SG (mean), Patients (N=162)
Sullivan (2007)[93]							0.635			EQ-5D (mean baseline) Total patients (N=280)
							0.715			EQ-5D (mean baseline) UK patients (N=29)

The Sandblom study was deemed most appropriate to use in the TA101 Docetaxel evaluation,[30] this and the Sullivan et al., (2007)[93] study are briefly summarised to explore their relevance to the present economic evaluation of AAP.

Sandblom et al., (2004)[95] conducted a postal survey in the Oestergoetland region, Sweden, in September 1999, to determine how HRQL is affected by approaching death. A questionnaire including the EuroQoI (EQ5D and EuroQol visual analogue scale, VAS), the BPI forms and eight specifically designed questions (relating to pain treatment, medications, civil state, and ease of contact of a medical professional if needed) was sent to a total of 1442 men with prostate cancer. 'Worst pain' was significantly higher in men dying of prostate cancer as compared to men dying of other causes. Pain did also interfere with daily functions to a much higher degree in those who died within the study period as compared to those still alive thereafter. The EQ-5D score for men who died of prostate cancer was 0.538 (confidence interval (CI) +/- 0.077), and 0.564 (CI +/- 0.067) for men who died of other causes. The score was considerably higher for men still surviving with prostate cancer, 0.770 (CI +/- 0.015). In terms of suitability of use in the economic

evaluation, the Sandblom study provides good estimates of HRQL in patients approaching death with prostate cancer, and therefore provides a good estimate of utility for the post-progression state in the model; the average time spent in this state was approximately 8 months in the model. Complications of prostate cancer significantly affecting quality of life will occur almost exclusively in the post-progression health state; these complications are often a signal of progression if experienced in a progression free patient.

In the COU-AA-301 study, FACT-P was not collected past the point of disease progression (treatment discontinuation), therefore an estimate of utility in the post-progression state was not available. Thus, the Sandblom et al.,(2004) study was used estimate utility in the post-progression health state. Utility values from the Sandblom study ranged from 0.58 in patients with 8-12 months of remaining survival to 0.46 in those with less than 4 months remaining survival. Given that mCRPC patients are likely to spend their last 6-8 months of life in the progressed health state (results of the economic model), a utility value of 0.50 was assigned to the progressed health state based on the average utility observed in the Sandblom et al. study for patients in the last 8 months of life. Additional sensitivity analyses have been conducted around these estimates.

A second study, Sullivan et al., (2007)[93] was an observational, multi-centre, multi-national cohort study (n=280) designed to explore HRQL (EORTC QLQ-C30, FACT-P and EQ-5D) in a mCRPC population. The average age of subjects in the study was 72 and the population was 98% Caucasian. The baseline EQ-5D for the total population was 0.635 and for the UK subset was higher at 0.715. The study captured QoL using these three measures at three further time-points (3, 6, and 9 months after baseline), however the study did not breakdown the analysis for those whose disease had progressed vs. those whose disease had not, therefore did not provide any additional data for the post-progression state.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The Sandblom study was used to determine post-progression state utilities in the model, but does not provide a suitable estimate of the progression free state that accurately reflects mCRPC population in the UK today. Specifically, the Sandblom study precedes, in time, the introduction of docetaxel, which altered the treatment pathway and outcomes for mCRPC patients. Hence, COU-AA-301 study subjects were likely fitter with higher QoL compared to those patients close to death in the Sandblom study. COU-AA-301 patients likely had higher functional status than patients in the Sandblom study; patients need a Karnofsky score >60% to receive docetaxel and only 10% of subjects in COU-AA-301 had an ECOG status <1. In addition, utilities for subjects in the progression free state in the model have been derived from mean scores prior to progression in COU-AA-301. Patients in the progression free state are not clinically progressing and therefore were unlikely to be greatly impaired by their disease at that point in time. This is in contrast to those subjects in the Sandblom study, which are a mixture of pre-progression and post-progression.

[redacted]

It should be noted that utility data from the Sandblom et al. (2004)[95] analysis was used to inform the baseline utility of mCRPC in the HTA of docetaxel commissioned by NICE.[72] Specifically, TA101 considered a baseline utility of mCRPC of 0.538, based on the mean utility over a patient's final year of life from this study. [redacted] The difference was probably due to the differences observed between the study populations. As mentioned above, the COU-AA-301 population was more likely fitter with a higher functional status than those in the Sandblom study due to their requirement to have had prior docetaxel. Further, the mean age of patients who died of prostate cancer in the Sandblom study was 76 years, versus 69 in the COU-AA-301 study. Additionally, the absolute values assumed here are consistent with a comparable population of chemo pre-treated breast cancer patients in a recent NICE appraisal.[116] Overall, the estimated pre-progression utility value of ([redacted]) appears consistent with the literature.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL

AEs associated with treatment of mCRPC are common. Toxicities with abiraterone acetate are generally manageable, and infrequently resulted in dose reductions, dose interruptions, or discontinuations.[15] In this regard, it was noted in the EPAR that the safety profile of abiraterone acetate is distinct from that typically experienced with conventional cytotoxic agents, such as docetaxel. These agents are frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, and indeed life-threatening. Specifically, with abiraterone acetate, the most frequently observed AEs such as hypertension or hypokalaemia are generally asymptomatic. Fluid retention/oedema or urinary tract infections may occur but are generally tolerable. Unlike the aforementioned cytotoxic agents, abiraterone acetate, does not have the propensity to induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia, alopecia, etc, which not only may be associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life which is particularly relevant in the context of therapy for patients with advanced cancers. A review of the literature identified several studies in metastatic cancers that indicate the impact of commonly occurring AEs, Table 33. In those studies reporting utilities for Grade 3/4 or severe AEs, the values ranged from 0.05 to 0.261.

Table 33. Disutility of Adverse Events from the published literature.

Source	Negreiro (2008)[117]	Lloyd (2006)[118]	Beusterien (2010)[119]	Ossa (2007)[120]	Grutters (2010)[121]	Doyle (2008)[122]	Nafees (2008)[123]	Swinburn (2010)[124]
Elicitation Method/Tool	EQ5D	SG	SG	TTO	EQ5D	SG	VAS and SG	TTO
Disease Area; AE Grade	NSCLC; Grade Unknown	MBC; Grade 3/4	CLL; Grade Unknown	Chemotherapy- related anaemia	NSCLC; Grade Unknown	NSCLC; "Severe"	NSCLC; Grade Unknown	MRCC; Grade 3
Diarrhoea	0.126	0.103					0.0468	0.261
Nausea	0.136						0.04802	0.255
Vomiting		0.103					0.04802	
Neutropenia	0.127						0.08973	
Febrile Neutropenia	0.257	0.15					0.09002	
Neuropathy	0.145							
Fatigue		0.115					0.07346	0.204
Asthenia		0.115						
Thrombocytopaenia								
Anaemia			0.09	0.25 - 0.38				0.119
Arthralgia						0.069		
Hypokalaemia								
Enema								
Hypertension								0.153
Dyspnoea					0.29	0.05		

Abbreviations: CLL = chronic lymphocytic leukaemia; EQ5D = EuroQol 5-Dimension; MBC = metastatic breast cancer; MRCC = metastatic renal cell carcinoma; NSCLC = non small cell lung cancer; SG = standard gamble; TTO = time trade-off; VAS = visual analog scale

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 34 Summary of quality-of-life values for cost-effectiveness analysis in the base case and ITT analyses.

	Base case		ITT			
State	**Utility value**	**SE**	**Utility value**	**SE**	**Reference in submission**	**Justification**
Pre-progression State (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected QoL in the pre-progression health state
Post-progression State	0.50	0.08	0.05	0.08	Sandblom et al (2004)[95]	Post-progression QoL was not captured in the COU-AA-301 trial after initial progression visit. Sandblom et al., provides the most roubst estimate of patient QoL in the literature.
On treatment utility gain for AAP and MP (base case)	[redacted]	[redacted]	[redacted]	[redacted]	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected the on treatment QoL experienced by subjects in the study
AE disutility (applied to MP arm only)	[redacted]	[redacted]	[redacted]	[redacted]	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected the disutility experienced by subjects when and AE occurred in the study

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

UK clinicians involved in the consensus meeting (methodology summarised in Section 6.3.5) qualitatively assessed the quality of life impact of the different Grade 3/4 AEs; differences identified are explored in sensitivity analyses

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Fluctuation of QoL may be expected in patients with mCRPC in this late stage of disease within the pre-progression or post-progression health states, however generally at this late stage of disease, QoL will decline. Within the COU-301-AA data collected on QoL (FACT-P, BPI and BFI) was collected at regular intervals during the pre-progression period. Results from this study demonstrate that pain and functioning declines as the disease progresses, Figure 24.

Figure 24.

As the progression definition used in the economic analysis utilises data collected across the progression free state, no further adjustment is required to account for variability over time for this health state. In the post progression health state it might be speculated that HRQL declines towards death and that truly terminal patients may not be captured within utility studies, as such the mean post-progression utility may be overestimated thought this would be a conservative assumption.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

No studies, other than COU-AA-301, were identified that specifically captured utility values for the comparators relevant to the decision problem in the post-chemotherapy population. As HRQL differences are analysed directly with the COU-AA-301 trial, we anticipate that all potential health effects for the AAP vs. PP comparison are captured prior to progression. Post-progression values were taken from the Sandblom studying Section 6.4.6.

6.4.13 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 entered the model into the pre-progression health state.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The model assumes a constant utility in both the pre-progression and post-progression health states, see section 6.4.11.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Utility values used in sections 6.4.3 to 6.4.8 have not been altered from the estimates calculated in the mapping analysis using data from the 'Updated' analysis of the COU-AA-301 study. The post-progression estimate from the Sandblom study has been used as reported in the study.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 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 relevant to the clinical management of mCRPC patients who have previously received docetaxel is the chemotherapy tariff, but only for the minority of patients (estimated from clinical opinion to be 20%[3]) who receive further treatment with chemotherapy.

NHS references costs used in the clinical management of the disease include outpatient and inpatient visits for treatment monitoring and chemotherapy infusion administration costs. Costs associated with treating grade 3/4 AEs include hospitalisation costs, outpatient treatment and clinical follow-up.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Whilst abiraterone acetate is not chemotherapy and therefore not associated with a chemotherapy tariff, this tariff is relevant to the MP comparator. Cost sources used in the model include:

- Drug costs for the interventions and concomitant medications were collected from the British National Formulary (v.61, March 2011)[125]

- Unit costs for chemotherapy administration, as well as clinical scheduled and unscheduled follow-up procedures were determined using the UK National Schedule of Reference Costs, Year 2009-2010.[126]

- Unit costs for Outpatient visits and Community Nurse visits were determined from the Unit Costs of Health and Social Care (2010).[127]

Resource identification, measurement and valuation studies

6.5.3 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 9.13, 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.

The systematic review previously described in Section 6.1 encompassed economic evaluations and studies of the burden and costs of advanced and metastatic prostate cancer. The review identified 19 potentially relevant publications; however only three of these included costs from a UK setting.

The primary objective of Oosterhof et al., (2003)[128] was to compare toxicity, subjective response rate, time to subjective progression and OS in subjects (n=203) with painful bone metastases of hormone-resistant prostate cancer (HRPC) treated with Strontium(89) or palliative local field radiotherapy with the usual radiotherapy regimen in four countries (Belgium, Denmark, Netherlands and UK). Although this study captured the costs associated with both treatments, the use of medical resources was similar between the two groups. One limitation of this study was that resource use data was only collected until disease progression and was not reported separately for UK subjects versus other countries. In addition, although this study is conducted in a castration resistant sample, only approximately 25% of these patients received chemotherapy during the study. For these reasons, this study was not considered relevant to the decision problem.

Oglesby et al., (2008)[65] characterised the hospital burden associated with metastatic bone disease (MBD) and SREs following breast cancer and prostate cancer. A UK database that captures 70% of hospitalisations across the UK was queried to explore all patients with an inpatient admission between January 2003 and March 2004. Patients were followed up for re-admissions until March 2006. This study, which is only available as a conference poster presentation, explored admission and re-admission rates across these two cancer types, and the average length of stay for prostate cancer patients with MBD & SREs was 43 days. The mean cost of admission was higher for prostate cancer patients with MBD & SREs compared to other reasons for admission (£3618 vs. £1871). Finally, Hechmati et al., (2011)[129] sought to determine the burden of bone metastases and health resource utilisation associated with SREs in patients with advanced cancers (breast, lung, prostate or multiple myeloma) in Germany, Italy, Spain, and the UK. This study did not report results separately for each of the cancer types (n=631), but reported that the mean length of stay for all SREs and individual SREs in the UK. As these events were not specifically attributed to prostate cancer, this study was not used to estimate resource use.

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

Using the methodology[3] outlined in section 6.3.5, England and Wales resource use estimates relating to dosing and duration for each treatment option (mitoxantrone, BSC and abiraterone acetate) and well as resource use associated with imaging diagnostic tests and clinical laboratory tests performed prior to, during and following disease progression for each treatment option were captured. In addition, the resource use associated with the treatment of Grade 3/4 AEs in the England and Wales was estimated.

Intervention and comparators' costs

6.5.5 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 6.2.2.

The list price of abiraterone acetate is £2930. Janssen is in the process of agreeing a Patient Access Scheme (PAS) with the Department of Health, which is reflected in the base case analysis in this submission. [redacted] A scenario analysis showing the cost-effectiveness of abiraterone acetate without the PAS is also provided as commercial in confidence. The cost of mitoxantrone is £100 per 20mg vial and the cost of prednisolone was £1.03 per 28 5mg-tablet pack.[125] The cost of concurrent prednisolone was included for all treatments, and was assumed to continue until death, even after chemotherapy was discontinued, for all patients.

Dosing used in the model for AAP and PP matched dosing in the COU-AA-301 clinical trial which reflects the doses recommended in the abiraterone acetate SPC.[14] For mitoxantrone, in which dosing is determined based on body surface area, a surface area of 2.02 m^2 was used, matching the average observed in the TROPIC trial.[12] All drug costs were converted to a 3-week model cycle. Vial reuse was not permitted for mitoxantrone, per the summary of product characteristics.

Table 35. Dosing regimens implemented in the economic model.

	Dose per administration	Dose Frequency	Administration Type	Doses per model cycle
Abiraterone	1000mg	Daily	Oral	21
Prednisolone	10mg	Daily	Oral	21
Mitoxantrone	24mg	Every 3 weeks	IV	1

All treatments other than prednisolone monotherapy are administered with concurrent prednisolone, 10 mg daily.

For mitoxantrone, it was assumed that patients would incur the cost of one outpatient visit per model cycle to administer therapy. Therefore an administration cost of £248.45 was applied (Code: SB12Z - deliver simple parenteral chemotherapy at first attendance).[126] These costs are summarised in Table 36.

Table 36. Unit costs associated with the technology in the economic model associated with acquisition and administration costs. Costs are expressed as per model cycle (3 weekly) cost per patient.

Items	AAP	Ref.	PP	Ref.	MP	Ref.
Mean cost of technology per 3 week cycle	[redacted]		£1.55	British National Formulary v.61[125]	£200 [a]	British National Formulary v.61[125]
Administration cost per 3 week cycle	[redacted]		-		£248.45	NHS reference costs: Code SB12Z[126]
Total	[redacted]		£1.55		£448.45	

[a] Vial reuse is not permitted; thus 2 vials are required for the dose required

Health-state costs

6.5.6 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 6.2.4.

Scheduled disease related clinical follow-up medical resource use

Costs of scheduled, disease related patient follow-up consisted of clinical visits, imaging diagnostic tests and clinical laboratory tests to monitor the status of disease in patients with mCRPC. To understand the UK standard practice in treating an average patient a consensus panel (methodology described in section 6.3.5) was used to obtain MRU values for the model.[3] In the absence of UK patient level data, this method is considered to be more reliable and robust than simple individual expert interviews. Unit costs for these regularly scheduled follow-up procedures were determined using the UK National Schedule of Reference Costs, Year 2009-2010 (UK Department of Health 2011), Table 37. Estimated MRU associated with each treatment is summarised in Table 38.

Table 37. Unit costs associated with scheduled follow-up visits (NHS reference costs 2009-10).[126]

Resource	Unit Cost	Reference	Code
Out-patient visit (consultant)	£166.00	Unit Costs of Health and Social Care 2010	800
Out-patient visit (nurse)	£37.00	Unit Costs of Health and Social Care 2010	10.4
Community nurse visit	£12.00	Unit Costs of Health and Social Care 2010	10.6
CT scan	£112.00	NHS reference costs 2009-10	RA10Z
Radiographic/MRI scan	£229.00	NHS reference costs 2009-10	RA03Z
ECG	£33.00	NHS reference costs 2009-10	DA01
Ultrasound	£55.00	NHS reference costs 2009-10	RA23Z
Bone scan	£180.00	NHS reference costs 2009-10	RA36Z
Full blood count	£3.06	NHS reference costs 2009-10	DAP823
Liver function test	£9.03	NHS reference costs 2009-10	DAP841
Kidney function test	£12.90	NHS reference costs 2009-10	DAP841
PSA	£1.29	NHS reference costs 2009-10	DAP841

Table 38. Estimated Scheduled MRU implemented in the model, following discussion in clinical consensus meeting.[3]

	Mitoxantrone (on treatment)	Abiraterone (first 3 months)	Abiraterone (months 4+)	1. Prednisolone 2. Mitoxantrone (off treatment)
Out-patient visit[a]	1 visit, every 3 wks	1visit, every 2 wks	1 visit, every month	1 visit, every 6 wks
CT scan	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks
Radiographic scan/MRI scan	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks
ECG	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks
Ultrasound	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks
Bone scan	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks	1 in 5% of patients, every 6 wks
FBC	1, every 3 wks	1, every 6 wks	1, every 6 wks	1, every 6 wks
Liver/Kidney function tests	1, every 3 wks	1 every 2 wks for liver tests, 1 every 4 wks for kidney tests	1, every 4 wks	1, every 6 wks
PSA	1, every 3 wks	1, every 6 wks	1, every 6 wks	1, every 6 wks

[a] Conducted by a clinical oncologist for mitoxantrone - on treatment, and alternate between clinical oncologist and nurse specialist for prednisolone, mitoxantrone-off treatment, abiraterone first 3 months, and abiraterone months 4+.

CT = computer tomography, MRI = magnetic resonance imaging, ECG = electrocardiogram, FBC = full blood count, PSA = Prostate specific antigen

Unscheduled event related medical resource use

The COU-AA-301 trial recorded resources consumed as a result of unplanned events while on treatment. Statistical analysis of these data was conducted to assess how unscheduled MRU (and therefore costs) differed between treatment arms, appendix 16. Total resource utilisation while patients were receiving treatment was very similar between abiraterone and prednisolone, which was independent of treatment duration. That is, while abiraterone postponed progression compared to prednisolone, medical resource utilisation was similar during the progression free period, indicating that resource utilisation was tied to progression rather than the duration of PFS. As a result, a one-off fixed cost for unplanned, event related resource utilisation in the model progression free health state was applied. Due to the absence of data specific to mitoxantrone treatment, we assumed that baseline resource utilisation on this treatment is equivalent to abiraterone, and that any incremental cost differences between abiraterone and mitoxantrone would be due to differing rates of Grade 3/4 AEs.

Table 39. List of health states and associated costs in the economic model. Pre-progression and post-progression MRU associated with clinical assessments is broken down into costs associated with scheduled and unscheduled visits. Values are presented as monthly cost per patient unless otherwise stated.

Health states	Items	Value	Reference in submission
Pre-progression (monthly cost)	MP arm on treatment cost (scheduled MRU)	[redacted]	Clinical consensus meeting, Table 38
	MP arm off treatment cost (scheduled MRU)	[redacted]	Clinical consensus meeting, Table 38
	AAP arm on treatment costs (scheduled MRU) First 3 months	[redacted]	Clinical consensus meeting, Table 38
	AAP arm on treatment costs (scheduled MRU) After 4 months	[redacted]	Clinical consensus meeting, Table 38
	PP arm (scheduled MRU)	[redacted]	Clinical consensus meeting, Table 38
	AAP and MP arm therapeutic use of G-CSF (0.3% of patients)	£686.38/model cycle	BNF v.61[125]
	All treatments (concomitant bisphosphonate use in 37% of patients)	£48.54	BNF v.61[125]
	All treatments: one time cost (unscheduled MRU)	[redacted]	COU-AA-301 MRU analysis, Appendix 16
Post-progression (monthly cost)	All treatments (scheduled MRU)	[redacted]	Clinical consensus meeting, Table 38
	All treatments (unscheduled MRU)	[redacted]	COU-AA-301 MRU analysis, Appendix 16
	All treatments (concomitant bisphosphonate use in 100% of patients)	£132.38	BNF v.61[125]
	All treatments: one time cost of subsequent treatment ([redacted])	[redacted] /pt	BNF v.61[125]

Concomitant medication use associated with treatment

In the COU-AA-301 trial, 36.67% of UK patients took bisphosphonates concurrently,[42] and a panel of UK oncologists and specialist nurses agreed that almost all mCRPC patients with symptomatic or progressive disease would receive bisphosphonates.[3] In the progression free health state a monthly cost of £48.54 was applied, corresponding to bisphosphonates (Zometa 4 mg infusion every 6 weeks, £183.30 per dose) utilised by 36.67% of patients. In the post progression health state a monthly cost of £132.38 was applied, corresponding to use by 100% of patients.

Granulocyte colony-stimulating factor (G-CSF) is an effective treatment option for febrile neutropaenia. Pegfilgrastim (Neulasta®) is the G-CSF considered in the model, as oncologists in the UK report that it is the most commonly used form.[3] Only therapeutic use (use of G-CSF in response to the occurrence of febrile neutropaenia) was considered in the model, as interviews conducted with UK oncologists actively treating mCRPC indicated that prophylactic use of G-CSF is very rare. The percentage of therapeutic use of G-CSF is based on the product of the rate of febrile study[12] (1%) and the prevalence of therapeutic G-CSF use among neutropaenia observed among patients receiving MP in the TROPIC patients with febrile neutropaenia agreed upon by UK oncologists, or 30%, for a total of 0.3%.[3] It was also assumed that if febrile neutropaenia occurs, it occurs after the first cycle of chemotherapy. Therefore, therapeutic G-CSF use would begin in cycle 2 and continue through the end of treatment. As a small amount of febrile neutropaenia ([redacted]) was observed in the AAP arm of COU-AA-301 study, therefore in the base case a similar amount of GCSF use was assumed for AAP.

[redacted]. It was assumed that [redacted]% of patients in each treatment arm would receive 3 cycles of cabazitaxel after progression, equivalent to

£3,944 per cycle for drug and administration. Given the toxicity profile of cabazitaxel, each patient would incur [redacted] in one-off incremental Grade 3/4 AE costs. Therefore the total one off cost attributed to those patients that subsequently received cabazitaxel was [redacted]

Terminal treatment costs

Resource use and associated costs typically spike in the months immediately prior to death for patients with prostate cancer.[130] Because OS differs by treatment for mCRPC, the effects of discounting leads to an incremental difference in terminal costs per treatment, and terminal costs are considered in the economic model. The medical resources utilised by mCRPC patients over their last 3 months of life were defined by clinical experts.[3] The oncologists agreed that the average patient would receive home care by a nurse twice per day (assumed once during the day and once in the evening), for 14 days each month. In addition the experts agreed that 50% of patients typically die in a hospital (palliative care unit assumed) 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 1 hour home care visit in both a day and evening settings (averages to £23.50 per hour) were obtained from the Unit costs of health and social care database, 2010.[127] Daily cost of both a hospice centre and a palliative care unit of a hospital was £119.00 (Inpatient, Hospital Specialist Palliative Care, 19 years +, code SD03A), based on the UK National Schedule of Reference Costs.[126] In summary, terminal costs according to these assumptions were [redacted] per patient for each treatment.

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. 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 6.2.2.

A statistical analysis of unplanned, event related medical resource utilisation collected in the COU-AA-301 trial was used to determine the baseline rate of resource utilisation for AAP and PP, Appendix 16. In the absence of detailed data for MP, the baseline rates of medical resource utilisation were assumed to be equal to that of AAP. To address the impact of differences in AE rates, we assigned costs of treating Grade 3/4 AEs to the incremental rates of each event versus abiraterone acetate for mitoxantrone. An advisory board composed of UK oncologists familiar with treating Grade 3/4 AEs was interviewed to identify resources utilised in treating such events.[3] The advisory board estimated the percentage of patients treated in each setting, as well as the likely medications prescribed. Unit costs of treatment in these settings were determined according to the UK National Schedule of Reference Costs, Year 2009-2010.[126] Medication cost is only applied to patients who were not treated as inpatient cases to avoid double counting. The treatment cost for each AE is the weighted average of cost that patients incur in the different settings plus the medication cost as applicable. The medication cost was calculated based on the medication type, dose and duration suggested by the advisory board. Unit drug cost information is obtained from British National Formulary v.61.[125]

Table 40. MRU associated with Grade 3/4 AEs

	% Treated inpatient	% Treated as oncologist clinic day case	% Treated by GP	% Treated by nurse visit or phone call	Follow-up	Medication[a]
Neuropathy	0%	100% (1-2 visits)	0%	A few additional nurse visits	None	Gabapentin (900mg three times a day)
Neutropaenia	0%	100%	0%	0%	1-2 oncologist visits	No
Febrile Neutropaenia	100% (5-7 days)	0%	0%	0%	1-2 oncologist visits	G-CSF 300mcg once daily for 1 week for 30% of the patients, Tazocin 4.5g three times a day iv for 5 days, iv imipenem- Primaxin®[b]
Thrombocytopaenia	20% (platelet transfusion needed)[c]	80%	0%	0%	1 oncologist visit for hospitalised patients	No
Anaemia	30% (inpatient transfusion needed)[c]	70%	0%	0%	1 oncologist visit for hospitalised patients	Outpatient transfusion 2-3 units for 70% of patients
Oedema	25%	75%	0%	0%	1 oncologist visit	Furosemide 40-20mg once daily (1-2 weeks), iv fluid (Sodium Chloride 0.9% IV infusion)
Hypokalaemia	50%	50%	0%	0%	1 oncologist visit	Sando-K®, iv KCl
Hypertension[c]	0%	50%	50%	0%	1 oncologist visit	Clonidine 0.1 mg orally, Amlodipine 5-10 mg a day
Arthralgia	0%	34%	66%	0%	1 GP visit	OxyNorm® 5 mg every 4-6 hrs, Acetaminophen - Paracetamol
Asthenia	0%	0%	0%	100%	No	Dexamethasone (2-4mg) for 6 days
Diarrhoea (Grade 3)[f]	50%	50%	0%	0%	1 oncologist visit for hospitalised patients	Loperamide 2mg as needed, iv fluid
Dyspnea[e]	NA	NA	NA	NA	NA	NA
Fatigue	0%	0%	0%	100%	No	Dexamethasone (2-4mg) for 6 days
Nausea	0%	100%	0%	0%	No	Domperidone 20mg ad needed or four times a day
Vomiting	80%	20%	0%	0%	1 oncologist visit for hospitalised patients	Ondansetron 8mg twice daily for 3-4 days, Maxalon, iv fluid

a. Medication duration is assumed to be 2 weeks unless specified, to match the average duration of a grade 3/4 adverse event.
b. G-CSF cost is considered separately in 5.9.1.2, and thus it is not included in calculating the medication cost of febrile neutropaenia.
c. Inpatient blood transfusion is covered as part of the inpatient stay cost, and incurs no additional cost.
d. All hypertension events are assumed to be grade 3, since no grade 4 event is observed in the COU-AA-301 trial.
e. This is rarely an isolated event, so it is treated with other events with no additional cost.
f. No Grade 4 diarrhoea was observed in either abiraterone + prednisolone or mitoxantrone + prednisolone

Table 41 List of adverse events and summary of costs included in the economic model

AEs	Items	Value	Reference in submission
Neuropathy	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Neutropaenia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Febrile Neutropaenia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Thrombocytopaenia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Anaemia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Oedema	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Hypokalaemia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Hypertension	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Arthralgia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Asthenia	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Diarrhoea	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Dyspnoea		[redacted]	Section 6.5.7
Fatigue	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Nausea	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7
	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7
Vomiting	Follow-up visits	[redacted]	Section 6.5.7
	Treatment cost	[redacted]	Section 6.5.7

	Medication cost (per 3 wks cycle)	[redacted]	Section 6.5.7
	Total	[redacted]	Section 6.5.7

Table 42. Total cost of Treating Grade 3/4 Adverse Events

AE	Treatment Cost/per event	Medication Cost[a]/per event	Total Cost/per event
Neuropathy	[redacted]	[redacted]	[redacted]
Neutropaenia	[redacted]	[redacted]	[redacted]
Febrile Neutropaenia	[redacted]	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Oedema	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]

a. Medication cost is only applied patients who were not treated as inpatient cases.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None

6.6 Sensitivity analysis

6.6.1 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.

Several scenario analyses have been conducted to explore the sensitivity of the model to key assumptions used in the model.

- ITT population: The data for the ITT population was used instead of the data from the 'One Prior Chemotherapy' population.

- PFS benefit for MP: In the base case it was assumed that MP did not have a PFS benefit compared to PP, based on the absence of comparative evidence to demonstrate otherwise. A scenario explores results when MP is assigned a PFS benefit compared to PP.

- Lower disutility assigned to those AEs that, following clinical opinion, were estimated to have a less impact on patient quality of life (neutropaenia and thrombocytopaenia).

- Scenario analysis without PAS.

Rationale for range of PFS HRs chosen for MP scenario analysis: In the base case analysis it was assumed that MP does not have a PFS benefit compared to PP, based on the absence of comparative evidence to demonstrate otherwise. These scenario analyses explore results when MP is given a PFS benefit compared to PP. HRs used in this sensitivity analysis are based on the estimated PFS HRs observed in the RCTs comparing MP to corticosteroids in chemotherapy naive populations.[57, 58] Neither of these studies published HRs, so these were estimated using the Parmar approach. The HRs explored in the following scenario analyses 0.77 (compared mitoxantrone + hydrocortisone vs. hydrocortisone in a chemotherapy naive population (Kantoff et al., (1999)[58]) and 0.90 (a figure representative of a scenario where MP is assigned some PFS benefit, but assuming that this benefit would be less than observed in the chemotherapy naive population. The HR observed in the Berry (2002)[57] study was not explored, as it is not clinically plausible that this HR would be observed in a post-chemotherapy population for MP.

Rationale for exploring lower disutilities for neutropaenia and thrombocytopaenia: Feedback from UK clinicians involved in the consensus meeting (methodology summarised in Section 6.3.5) concluded that for Grade 3/4 AEs two would have only some impact on patient quality of life (neutropaenia and thrombocytopaenia) whilst, the rest would have a significant impact on patient quality of life. The scenario analysis was conducted reducing the disutility of those AEs deemed to have less impact on quality of life (Table 44) from [redacted] to [redacted].

Table 43. Clinical judgement of the impact of grade 3/4 AEs included in the economic model.

GRADE 3/4 adverse events				
	No impact on a patient's quality of life	**Some impact on a patient's quality of life**	**Significant impact on a patient's quality of life**	**How long would their QoL be impacted?**
Neuropathy			xxxx	Several months
Neutropaenia		xxxx		7-14 days
Febrile Neutropaenia			xxxx	7-14 days
Thrombocytopaenia		xxxx		7-14 days
Anaemia			xxxx	7-14 days
Oedema			xxxx	7-14 days
Hypokalaemia			xxxx	7-14 days
Hypertension			xxxx	7-14 days
Arthralgia			xxxx	7-14 days
Asthenia			xxxx	Several months
Diarrhoea			xxxx	7-14 days
Dyspnoea			xxxx	7-14 days
Fatigue			xxxx	Several months
Nausea			xxxx	7-14 days
Vomiting			xxxx	7-14 days

6.6.2 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 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The model explores both structural and parameter uncertainty in both one-way and probabilistic sensitivity analyses. Key model drivers are tested through one-way sensitivity analysis and are summarised in Table 44. Appendix 17 explains the rational for choosing the Weibull projection as the parametric function to test in the sensitivity analysis for modelling overall survival. In summary, The Weibull was found to be the best fit for the AAP arm and log-normal for the PP arm; however using the log-normal for the placebo arm is problematic for long-term projections, as it produces very long tails with clinically implausible survival.

Table 44. One-way sensitivity analyses explored in the model.

Parameter	Baseline value	Alternate value	Justification
Time Horizon	10 years	4, 6, 8 years	All patients in the model would be expected to have died at 10yr.
Discount rate - costs	3.5%	0% - 6%	
Discount rate - benefits	3.5%	0% - 6%	
Overall survival approach	KM+10% cutoff+constant hazard projection	KM+10% cutoff+ Weibull projection	Sensitivity analysis explores using different extrapolation methods (Weibull vs constant hazard) and a later cutoff point (10%). Fitting a Weibull parametric Function to the entire data was also explored.
		KM+5% cutoff+ constant hazard projection	
		KM+5% cutoff+ Weibull projection	
		Parametric (Weibull-placebo, Weibull-AA)	
		Lower end of the 95% CI of KM	
		Higher end of the 95% CI of KM	
PFS approach	KM+5% cutoff + constant hazard projection	KM+5% cutoff+ Weibull projection	Alternative PFS extrapolation approaches (Weibull and 10% cutoff) were explored
		KM+10% cutoff+ constant hazard projection	
Median treatment duration - mitoxantrone	4 cycles	2 – 7 cycles	Clinical opinion suggests that the average number of mitoxantrone cycles that a patient at this stage of disease would be 4; it would not be expected that these patients would receive more than 7 cycles.
Pre-progression utility of mCRPC	[redacted]	0.538 (Collins, 2007)[72] 0.85 (Krahn, 2003)[113]	Range of values of mCRPC pre-progression as found in the literature
Utility increment during abiraterone acetate treatment per cycle	[redacted]	[redacted]	
Utility of metastatic CRPC post-progression	0.50	0.4 (-20%) 0.46 (Sandblom, 2004)[95] 0.6 (+20%) 0.70 (+40%)	Range of values of mCRPC post-progression as found in the literature
Utility decrement from grade 3-4 AEs	[redacted]	[redacted]	Higher utility decrement as identified for grade 3/4 AEs in the literature
Schedule follow-up costs		±50% on all costs	
Unscheduled, Event-Related Medical Resource Utilisation cost		±50% on all costs	
Subsequent treatment costs	consider subsequent treatment (cabazitaxel)	no subsequent treatment	
GCSF use	0.3% of MP and AAP patients receive GCSF at cycle 2+	no GCSF use	
Bisphosphonate use	in PFS, 37% receive 1 every 6 weeks, 100% in post progression	50% use in PFS and post progression	
Adverse Event costs - all		±50% on all costs	
Terminal care costs	[redacted]	£0 - (+20%)	

6.6.3 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 6.3.6, 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).

The model runs a probabilistic sensitivity analysis to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probability distributions and analyzed using Monte Carlo simulation (1000 iterations). In probabilistic sensitivity analysis, the uncertainties around parameters were estimated, including utility, treatment duration, OS, and non-drug costs. Table 45 indicates the parameters varied and the probability distributions used.

Table 45 Model parameters varied in the probabilistic sensitivity analysis

Parameter	Distribution
Overall survival Kaplan Meier	Normal
Progression-free survival Kaplan Meier	Normal
Concomitant medication costs	Gamma
G-CSF costs	Gamma
Unscheduled progression free MRU	Gamma
Unscheduled post-progression MRU	Gamma
Subsequent treatment costs	Gamma
Scheduled follow-up costs	Gamma
Baseline Utility of mCRPC	Beta
Incremental Treatment Effect	Beta
Disutility Per Grade 3/4 Adverse Event	Beta
Utility of mCRPC – Progressed	Beta

6.7 Results

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), 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.

All results presented in the base case analysis use the 'Updated' data, are for patients who have received one prior docetaxel-based chemotherapy regimen ('One Prior Chemotherapy') and use the [redacted] the patient access scheme. Clinical results for median incremental PFS and OS for this population are similar to the mean results generated by the model for the AAP vs. PP comparison. In the model, the incremental mean OS is less than the incremental median OS observed in the trial. No clinical data for MP vs. PP comparison are available.

Table 46. Summary of model results compared with clinical data for AAP vs. PP ('One Prior Chemotherapy').

Outcome	Clinical trial result	Model result
Incremental Progression-free survival (years)	Median ([redacted])	[redacted]
Incremental Overall survival (years)	Median ([redacted])	[redacted]

Table 47. Summary of model results for AAP vs. MP; clinical trial comparison is not available ('One Prior Chemotherapy')

Outcome	Clinical trial result	Model result
Incremental Progression-free survival (years)	Not available	[redacted]
Incremental Overall survival (years)	Not available	[redacted]

6.7.2 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.

Not applicable.

6.7.3 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.

Not applicable.

6.7.4 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. For example:

Table 48 Model outputs by clinical outcomes and costs AAP

	LY	QALY	Cost (£)
Progression-free state	[redacted]	[redacted]	[redacted]
Post-progression state	[redacted]	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table 49 Model outputs by clinical outcomes and costs PP

	LY	QALY	Cost (£)
Progression-free state	[redacted]	[redacted]	[redacted]
Post-progression state	[redacted]	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year			

Table 50 Model outputs by clinical outcomes and costs MP

	LY	QALY	Cost (£)
Progression-free state	[redacted]	[redacted]	[redacted]
Post-progression state	[redacted]	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year			

The disaggregated outcomes and costs for the PFS and PPS states are presented in the tables above for each comparator. AAP is associated with more life years and QALYs than PP and MP in the PFS state, however is associated with slightly less life years and QALYs in the post-progression state. In the PFS state, the cost of AAP exceeds that of PP and MP, whereas MP has higher PPS costs that AAP or PP.

6.7.5 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.

The model predicts that AAP is associated with an incremental QALY gain of [redacted] and [redacted] compared to PP and MP, respectively Table 51 and Table 52.

Table 51 Summary of QALY gain by health state AAP vs. PP

Health state	QALY (AAP)	QALY (PP)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 52 Summary of QALY gain by health state AAP vs. MP

Health state	QALY (AAP)	QALY (MP)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 53 Summary of costs by health state AAP vs. PP

Health state	Cost (AAP)	Cost (PP)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 54 Summary of costs by health state AAP vs. MP

Health state	Cost (AAP)	Cost (MP)	Increment	Absolute increment	% absolute increment
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 55 Summary of predicted resource use by category of cost AAP vs. PP

Item	Cost intervention (AAP)	Cost comparator (PP)	Increment	Absolute increment	% absolute increment
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-medication cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unplanned event related MRU cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scheduled, follow-up MRU cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 56 Summary of predicted resource use by category of cost AAP vs. MP

Item	Cost intervention (AAP)	Cost comparator (MP)	Increment	Absolute increment	% absolute increment
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-medication cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unplanned event related MRU cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3/4 AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scheduled, follow-up MRU cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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					

Table 57. Summary of Costs and Outcomes from the Model

	AAP	PP	MP
Cost Components (£)			
Progression free health state	[redacted]	[redacted]	[redacted]
Drug	[redacted]	[redacted]	[redacted]
Concomitant Drug	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Adverse event management	[redacted]	[redacted]	[redacted]
Follow-up visits	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Drug	[redacted]	[redacted]	[redacted]
Adverse event management	[redacted]	[redacted]	[redacted]
Follow up visits	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Terminal	[redacted]	[redacted]	[redacted]
TOTAL COSTS	[redacted]	[redacted]	[redacted]
Health Outcomes			
LYs - On treatment survival	[redacted]	[redacted]	[redacted]
LYs - Progression free survival	[redacted]	[redacted]	[redacted]
LYs - Overall survival	[redacted]	[redacted]	[redacted]
QALYs - Progression free	[redacted]	[redacted]	[redacted]
QALYs - Progressive disease	[redacted]	[redacted]	[redacted]
TOTAL QALY	[redacted]	[redacted]	[redacted]

Base-case analysis ('One Prior Chemotherapy' population)

6.7.6 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.

Table 58. Base case results ('One Prior Chemotherapy' population)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£170,550	Extended domination by AAP
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£52,851
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

The base case estimates an ICER of £52,851 when AAP is compared to PP. In contrast, in the comparison between MP and PP, there is a smaller increase in incremental costs [redacted] resulting in an ICER of £170,550.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table 59. One way sensitivity results

Parameter	Baseline Value	Alternate Value	ICER vs. PP (£/QALY)	ICER vs. MP (£/QALY)
All parameters at baseline values			**52,851**	**46,617**
Time Horizon	10 years	4 years	57,057	50,146
		6 years	54,066	47,646
		8 years	53,141	46,863
Discount rate - costs	3.5%	0%	55,309	49,142
		6%	51,279	45,005
Discount rate - benefits	3.5%	0%	49,164	43,252
		6%	55,461	49,006
Overall survival approach	KM+10% cutoff+constant hazard projection	KM+10% cutoff+Weibull projection	56,484	49,817
		KM+5% cutoff+constant hazard projection	54,195	47,796
		KM+5% cutoff+Weibull projection	57,298	50,537
		Parametric (Weibull-placebo, Weibull-AA)	56,339	49,691
		Lower end of the 95% CI of KM	50,679	44,516
		Higher end of the 95% CI of KM	55,438	48,886
PFS approach	KM+5% cutoff+constant hazard projection	KM+5% cutoff+Weibull projection	53,301	46,878
		KM+10% cutoff+constant hazard projection	53,091	46,755
Median treatment duration - mitoxantrone	4 cycles	2 cycles	-	50,128
		7 cycles	-	43,849
Baseline utility of mCRPC	[redacted]	0.538 (Collins, 2007)	77,040	69,640
		0.85 (Krahn, 2003)	48,451	42,548
Utility increment during abiraterone acetate treatment per cycle	[redacted]	[redacted] (-20%)	54,353	48,014
		[redacted] (+20%)	51,708	45,556
Utility of mCRPC post progression	0.50	0.4 (-20%)	51,421	45,290
		0.6 (+20%)	54,364	48,024
		0.46 (Sandblom 2004)	52,270	46,077
		0.70	55,965	49,518
Utility Grade 3/4 AEs	[redacted]	[redacted]	-	45,983
Scheduled follow-up costs		-50%	51,147	45,699
		50%	54,555	47,534
Unscheduled, event-related MRU cost		-50%	53,486	47,285
		50%	52,217	45,948
Subsequent treatment costs	14% received cabazitaxel	no subsequent treatment	52,930	46,700
GCSF use	0.3% of mitoxantrone and abiraterone pts receive GCSF at cycle 2+	no GCSF use	52,758	46,541
Bisphosphonate use	In PFS, 37% receive 1 every 6 weeks, 100% in post progression	50% use in PFS and post progression	53,347	47,139
Adverse event costs - all		-50%	-	47,179
		50%	-	46,054
Terminal care costs	[redacted]	£0	52,960	46,731
		(+20%)	52,829	46,594

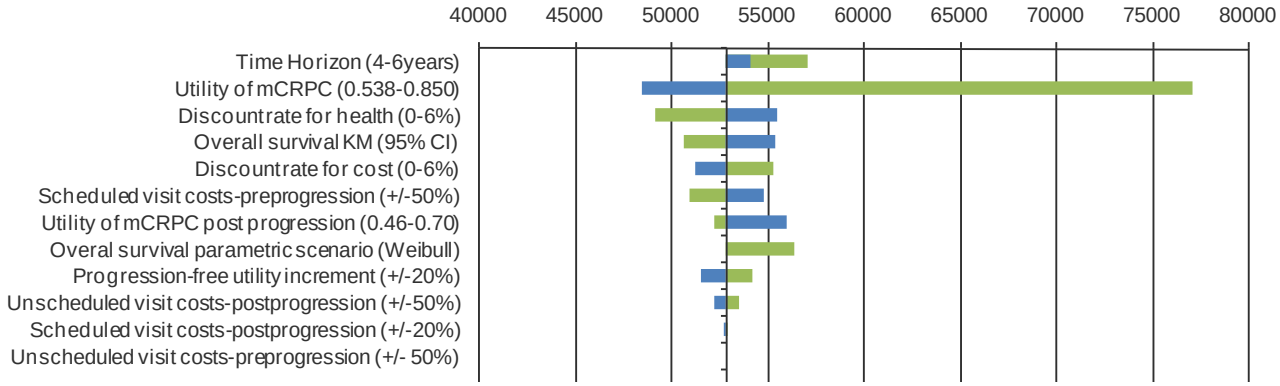

Figure 25. Sensitivity analysis: Tornado diagram AAP vs. PP comparison

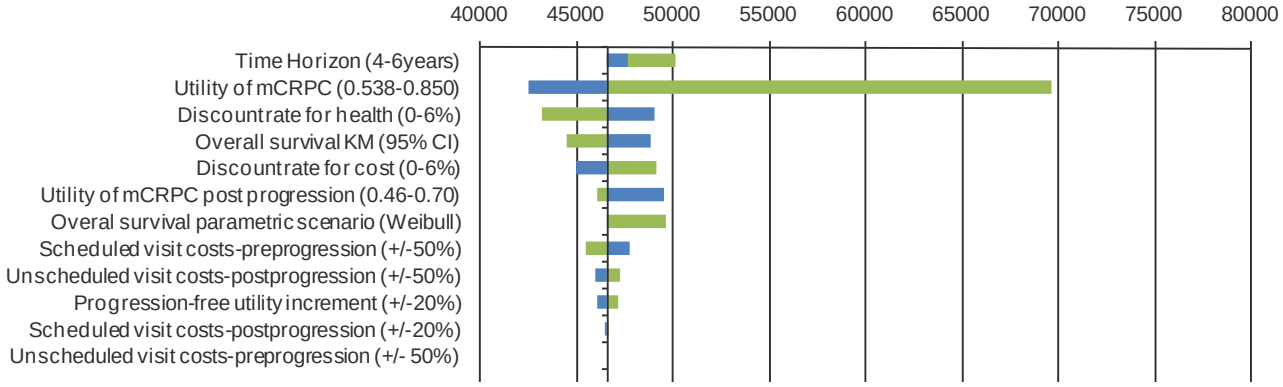

Figure 26. Sensitivity analysis: Tornado diagram for AAP vs. MP analysis

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis is presented for the base case in Figure 27 and Figure 28.

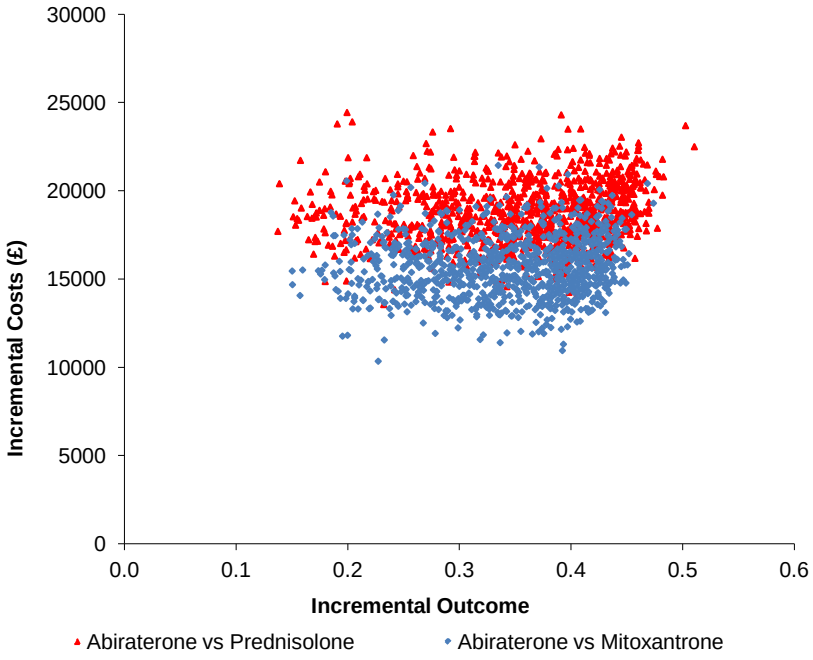

Figure 27 PSA cost-effectiveness scatter plot ('One Prior Chemotherapy')

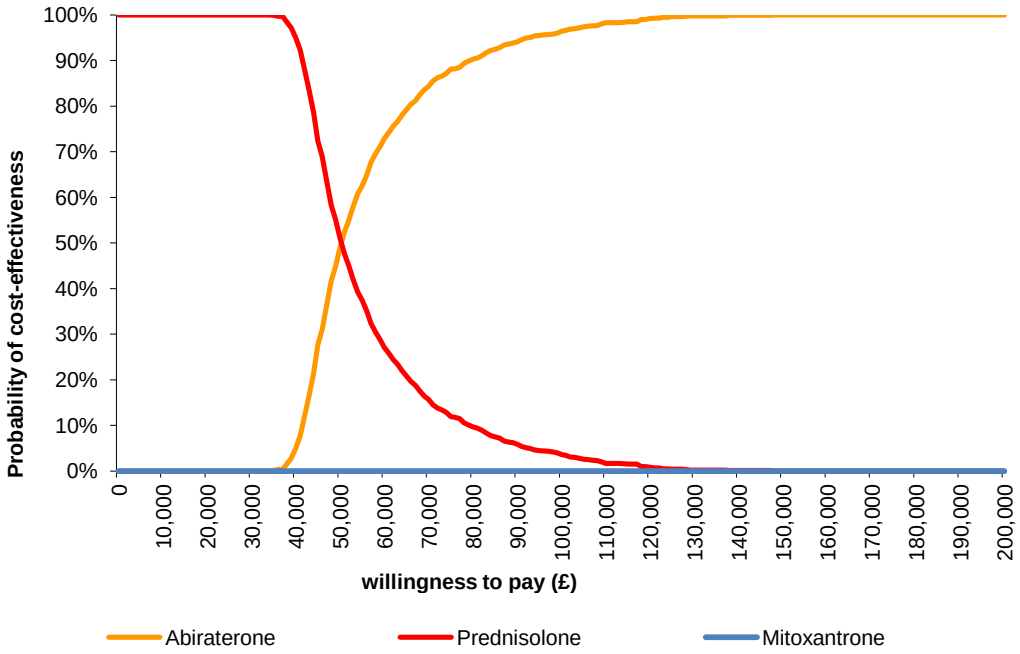

Figure 28. Cost-effectiveness acceptability curves ('One Prior Chemotherapy')

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

ITT population

Table 60. Results based on ITT population

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£186,086	Extended domination by AAP
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£63,233	£63,233
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Assume that MP does have a PFS benefit

The HRs explored in the following scenario analyses were 0.77 (Kantoff et al., (1999)[58]) and 0.84, rationale in section 6.6.1.

Table 61. Results based on scenario whereby MP PFS vs. PP PFS HR = 0.77

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,038	£21,038
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£62,843
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 62. Results based on scenario whereby MP PFS vs. PP PFS HR = 0.90

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60.606	Extended domination by AAP
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£52,851
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Reweight AEs of lower impact

Applying a reduced disutility value ([redacted]) for the two Grade 3/4 AEs (neutropaenia and thrombocytopaenia) that the consensus meeting felt would only have some impact on patient QoL as opposed to a 'significant impact'. This analysis has a very minor impact on results.

Table 63. Results based on scenario reducing the disutility assigned to Grade 3/4 neutropaenia and thrombocytopaenia AEs

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
PP	[redacted]	[redacted]	[redacted]					
MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,416	Extended domination by AAP
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,851	£52,851
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Scenario analysis without PAS

[redacted]

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
[redacted]	[redacted]	[redacted]	[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								

6.7.10 What were the main findings of each of the sensitivity analyses?

The probabilistic sensitivity analysis for the base case is summarised in Table 64. At a QALY threshold of £50,000 the probability that AAP is the most cost-effective option is 49%, at a QALY threshold of £55,000 the probability increases to 63%.

Table 64. Summary of PSA results

	PP	MP	AAP
£45,000	72%	0%	28%
£50,000	51%	0%	49%
£55,000	37%	0%	63%
£60,000	27%	0%	73%

The majority of cases within the deterministic sensitivity analyses indicated that the results were relatively stable across a range of assumptions. Within most of the assumptions

tested, ICERs for AAP were similar to other oncology products that were accepted by NICE under End of Life Criteria. . A 10% lower utility of mCRPC in the progression free state and a shorter time horizon and the OS have the greatest impact on the model.

As the efficacy estimates for AAP vs. PP were derived directly from the COU-AA-301 study (which has a long follow-up), there is a high degree of certainty around these key model variables for this comparison. The area under the Kaplan-Meier curve itself provides the best estimate of mean OS during the trial follow-up period; sensitivity analysis explored the impact of separately fitting parametric Weibull curves to the data. This parametric approach increased the ICER to £56,339 vs PP. Further scenario analyses explored varying the cut-off point for the KM data prior to extrapolation using the constant hazard rate (£54,195/QALY) and also explored using Weibull extrapolation (£56,484/QALY).

Due to the lack of comparative evidence evaluating the effectiveness of MP in a post-chemotherapy population, there is much uncertainty around the comparative efficacy of MP for both OS and PFS. Clinical opinion strongly suggests that MP does not have either an OS or PFS benefit over PP, but may offer some benefit with respect to pain. This opinion is reflected in the low use of MP in this population in England and Wales.

The deterministic analysis suggested that different assumptions regarding post-progression mCRPC utility and resource use costs had a limited impact on cost-effectiveness; in the sensitivity analysis varying this parameter from 0.40 to 0.70 results in an ICER range for AAP vs PP of £51,421 to £55,965/QALY. Progression free utility had a more important impact on cost-effectiveness, however due to the fact that these utility values are derived from the COU-AA-301 study and the fact that they are closely aligned with values from the Sandblom study (in those that survived longer than 16 months) and other literature, there is a high degree of certainty that the true progression free utility for this population is close to the [redacted] is a value used in the model.

6.7.11 What are the key drivers of the cost-effectiveness results?

As discussed above, the key drivers of the model are the parameters with a high degree of certainty around them as these values were obtained directly from the COU-AA-301 study; OS and progression free utility values.

6.8 Validation

6.8.1 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.

Prior to determining final results, the structure and programming of the completed Microsoft Excel model was validated by two modelling experts not involved in this study, and a variety of stress tests were performed to ensure that the model results were reflective of the inputs entered. For example, both extreme values and equal values across treatment arms were input and actual results were compared against results expected from a properly functioning model. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy the discrepancy.

An external review by three independent Health Economists was also carried out during the model development phase.

6.9 Subgroup analysis

6.9.1 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 due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The decision problem specified that three subgroups be explored: ECOG status, extent of prior taxane exposure and time since taxane treatment. Both ECOG status and number of prior chemotherapies were stratification factors and were pre-specified sub-group analyses within the 'Primary' analysis. For the reasons outlined in section 5.5.3, the 'One Prior Chemotherapy' population has been used as the base case in the economic evaluation. Although, there is no statistically significant difference between the 'One Prior Chemotherapy' subgroup and the >1 prior chemotherapy subgroup, the 'One Prior Chemotherapy' population (70% of subjects in the COU-AA-301 study) is more likely reflective of the UK population that will receive abiraterone acetate as per the licence. Hence this analysis has been presented as the base case and not as a subgroup in this section.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

6.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not applicable.

6.9.5 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 4.

Two of the subgroups defined in the decision problem were not explored in the clinical or economic evaluation: ECOG status and time since taxane treatment. As discussed in Section 5.5.3, subgroup analyses determined that those with only one prior line of chemotherapy ('One Prior Chemotherapy') or ECOG 0-1 have a significantly lower risk of death.

[redacted] Baseline data on time since prior treatment was not a pre-specified stratification factor and therefore it is not possible to explore subgroups with different time since taxane treatment as requested in the scope.

6.10 Interpretation of economic evidence

6.10.1 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?

There are no published economic models exploring the cost-effectiveness of the intervention or the comparators in the post-docetaxel population.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The results presented in the base case are reflective of the potential outcomes expected in the UK patient population.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the evaluation:

The model is based on data from the COU-AA-301 study; a methodologically robust trial with a long follow-up period (20.2 months) that compares the new treatment, APP, against the major comparator of interest in the UK setting. 'Updated' COU-AA-301 data presented in this submission captures 67% of all deaths and nearly all progression events. At this time point, patients were not permitted to cross-over and therefore no cross-over adjustments were required, which would introduce additional uncertainty to the model.

A comprehensive systematic review of the literature was conducted in an attempt to identify additional studies that may contribute to the evidence base of comparative effectiveness for treatments listed in the decision problem. Estimates of the relative effectiveness of AAP vs. the comparator of primary interest, PP, were obtained directly from COU-AA-301 study; indirect comparisons were not required.

The cost-effectiveness model was developed using established methodology that has previously been used in other late advanced and metastatic cancers.[83, 84] Goodness of fit was explored extensively for the comparators used in the model for key model parameters (OS and PFS) and extensive sensitivity analyses carried out around the extrapolation of

the data beyond the trial. Utility values for the progression-free state were estimated using QoL data directly collected from patients in the COU-AA-310 study.

Extensive probabilistic and deterministic sensitivity analyses were performed and the model was validated internally by extensive testing of the model by the developer and was also critiqued by an external expert in health economics during the development process.

The economic evaluation was consistent with the NICE critical appraisal checklist:

- The decision problem was consistent with the scope
- Comparators included all relevant treatments currently used in the NHS
- An NHS perspective on costs was employed
- All relevant health effects were considered (OS, PFS, AEs, treatment benefit)
- A cost effectiveness analysis was employed
- QALYs were the primary measure of health benefits
- The primary source of data for measurement of HRQL is FACT-P data collected in COU-AA-301
- A 3.5% discount rate was used for costs and health effects in the calculation of cost-effectiveness

Another major strength of the model is the robustness of the ICER to the sensitivity analyses.

Limitations of the evaluation:

As is common in economic evaluations, the present analysis is based on several assumptions. The biggest limitations of the analysis relate to the comparison with MP. There is a complete lack of evidence to establish, with any certainty, the relative efficacy and rate of AEs for MP compared to PP and AAP in the population of interest. There is no comparative evidence in the post-chemotherapy population comparing MP to PP or other BSC, and clinical opinion is that there is little benefit for MP in such patients other than potential pain palliation.

This evaluation also modelled the impact of subsequent therapy (specifically, [redacted] of patients in each arm were assumed to receive cabazitaxel). This assumption is based on the number of patients that went on to receive chemotherapy in the UK following on from the COU-AA-301 study, but it is unknown what proportion of patients would receive subsequent chemotherapy and whether in the future patients in on PP would be more likely to receive subsequent chemotherapy than those in AAP.

Estimates of costs relating to administration, monitoring and treatment of adverse events were collected from a UK clinical advisory board,[3] as these costs are difficult to capture within the constraints of a clinical trial and the literature search revealed little published evidence relevant to UK clinical practice. The model was not found to be sensitive to alterations in these assumptions.

Data on post-progression utility was not collected in COU-AA-301 and therefore a systematic review of the literature was conducted to identify an estimate of post-progression utility. The estimate chosen was at the higher end of the values reported in the literature and appears to be aligned with the pain, SREs and co-morbidities that these patients suffer in the last months of life.

What is not captured in the model:

QoL and MRU were not captured after the point of progression in the COU-AA-301 study and as AAP showed improved QoL in the pre-progression period, there may be some post-progression treatment benefits related to QoL and subsequent MRU costs that are not captured in the model. Similarly, AAP reduced the number of SREs and delayed time to first SRE, however were not consistently captured post-progression in the COU-AA-301 study. Therefore any benefit AAP may have regarding SREs that occur post-progression are not captured in the model. As discussed previously, SREs are associated with a significant decrease in patient QoL and significant costs.

6.10.4 End of life consideration

ICERs in the base case were similar to other cancer drugs recommended by NICE that have met End of Life (EoL) Criteria. The case for abiraterone acetate to be considered by NICE under the Supplementary Advice on appraising EoL medicines is presented below:

1) **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**

   The prognosis of mCRPC patients is poor; The five-year survival rate is significantly 31% in patients with metastatic disease.[5] The control arms of the TROPIC[12] and COU-AA-301[13]) studies indicate that after 1st line docetaxel treatment patients have a short life expectancy of approximately one year.

2) **The treatment is licensed, or otherwise indicated, for small patient populations**

   Of the 4,400 mCRPC patients estimated to receive docetaxel in the UK, it is estimated that approximately 75% these men would be eligible for treatment with abiraterone (3,300 men). It is estimated that no more than 50% of these men would actually receive treatment with abiraterone acetate.

3) **The treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment**

   Abiraterone acetate offers this population a 4.6 month increase in median overall survival compared to best supportive care (BSC).[13] The economic model estimates that the mean OS that could be expected for patients in England and Wales would be [redacted] years or [redacted] months.

6.10.5 What further analyses could be undertaken to enhance the robustness/completeness of the results?

[redacted]

[redacted]

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 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.

In 2006, NICE estimated that were 10,448 men with mCRPC in England and Wales; 0.0195% of the population;[1] using 2011 population estimates,[2] this equates to 10,856 men and could be expected to increase to 11,238 in 2016. Of these, clinical opinion estimates that 40%[3] will receive treatment with docetaxel (4,300 men). This estimate is aligned with a recent publication, whereby the number of men receiving chemotherapy increased from 11% in 2002 to 33% in 2008 within the Thames Valley Cancer Network.[28] This figure is also aligned with the NICE's estimates of the proportion of patients that would receive docetaxel following its introduction (45%).[1]

Of the 4,300 men estimated to receive docetaxel, it is estimated that approximately 75% these men would be eligible for treatment with abiraterone (3,300 men), a figure which accounts for those patients that may die on docetaxel treatment, may have rapid deterioration on docetaxel (not be suitable for further treatment) or those men in whom abiraterone acetate may be contraindicated or unsuitable. This figure of 75% is based on the number of patients surviving treatment on docetaxel at 1 year.[29]

The estimated number of patients with mCRPC eligible for treatment with AAP is shown in Table 65. It should be noted that the eligible patient population is representative of the population presented as the economic base case, the 'One Prior Chemotherapy' population.

Table 65. Eligible patient population for treatment of mCRPC patients, post-docetaxel.

	2011	2012	2013	2014	2015	2016
Population of England and Wales	55,610,000	56,001,400	56,392,800	56,784,200	57,175,600	57,567,000
Estimated number of mCRPC patients	10,856	10,932	11,009	11,085	11,161	11,238
% receiving docetaxel	*40%*	*45%*	*50%*	*50%*	*50%*	*50%*
Number receiving docetaxel	4,342	4,919	5,504	5,542	5,581	5,619
Assume 75% of these are eligible for abiraterone	3,257	3,690	4,128	4,157	4,186	4,214
Eligible patient population	3,257	3,690	4,128	4,157	4,186	4,214

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

The budget impact of current treatment is based on 80% of patients receiving PP and 20% receiving MP. In reality, a proportion of the PP patients may be involved in clinical trials for future therapies or be receiving non-NICE approved drugs funded through the CDF.

7.3 What assumption(s) were made about market share (when relevant)?

These estimates are based on the assumption of AAP receiving positive NICE guidance in Q2 2012. The future budget impact assumes that the majority of patients not treated with AAP would be treated with PP; MP would only be a treatment option for 5% of the patients. It is estimated that abiraterone would reach a peak market share of 46% in 2013 and assumes other competitors coming to market would take a share of the PP market.

	2012	2013	2014	2015	2016
Estimated Market Share	27%	46%	46%	46%	46%

7.4 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 for AAP were aligned with the median treatment duration from the COU-AA-301 trial of 8 months. Costs of treatment and monitoring associated with AAP, PP and MP are outlined in section 6.5.

No additional costs related to AEs are included, as AAP is assumed to have no incremental impact on the cost of treating AEs in this patient population when compared to MP and PP.

7.5 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 can be found in section 6.5.

7.6 Were there any estimates of resource savings? If so, what were they?

It was assumed that the introduction of abiraterone acetate in this patient population would not be associated with any resource savings.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

Without the PAS, assuming the positive NICE guidance on AAP is available in late Q2 2012, and that abiraterone achieves a market share of 27% in this year, the incremental budget impact would be £22 million. The maximum budget impact to the NHS could be expected in 2016; £44.6 million. With the PAS, the incremental budget impact would be [redacted] in 2012 increasing to a maximum budget impact in 2016 of [redacted]

Table 66. Overall budget impact for the NHS in England and Wales without patient access scheme.

mCRPC post-docetaxel patient population	**2012**	**2013**	**2014**	**2015**	**2016**
	3690	4128	4157	4186	4214
Future Treatment of mCRPC patients post-docetaxel	**2012**	**2013**	**2014**	**2015**	**2016**
AAP treatment costs					
Market Share	27%	46%	46%	46%	46%
Patient numbers	996	1899	1912	1925	1939
AAP treatment cost (£2930/mnth/pt)	£ 23,350,823	£ 44,512,145	£ 44,821,086	£ 45,130,027	£ 45,438,968
AAP monitoring cost (£1587.72/pt)	£ 1,581,680	£ 3,015,052	£ 3,035,978	£ 3,056,905	£ 3,077,831
Total AAP cost	£ 24,932,502	£ 47,527,197	£ 47,857,064	£ 48,186,932	£ 48,516,799
PP treatment costs					
Market Share	68%	49%	49%	49%	49%
PP treatment cost (£2.25/mnth/pt)	£ 45,161	£ 36,411	£ 36,664	£ 36,916	£ 37,169
PP monitoring cost (£914.24/pt)	£ 2,293,770	£ 1,849,351	£ 1,862,187	£ 1,875,022	£ 1,887,858
Total PP costs	£ 2,338,931	£ 1,885,762	£ 1,898,850	£ 1,911,939	£ 1,925,027
MP treatment costs					
Market Share	5%	5%	5%	5%	5%
MP treatment costs (£800/pt)	£ 590,338	£ 660,516	£ 665,100	£ 669,684	£ 674,269
MP monitoring costs (£993.80/pt)	£ 183,337	£ 205,131	£ 206,555	£ 207,979	£ 209,403
Total MP costs	£ 773,675	£ 865,647	£ 871,655	£ 877,663	£ 883,671
Budget Impact (Future Treatment)	**£ 28,045,109**	**£ 50,278,606**	**£ 46,466,086**	**£ 24,787,984**	**£ 22,848,246**
Current Treatment of mCRPC patients post-docetaxel	**2012**	**2013**	**2014**	**2015**	**2016**
PP treatment costs					
Market Share	80%	80%	80%	80%	80%
PP treatment cost (£2.25/mnth/pt)	£ 53,130	£ 59,446	£ 59,859	£ 60,272	£ 60,684
PP monitoring cost (£914.24/pt)	£ 2,698,553	£ 3,019,349	£ 3,040,305	£ 3,061,261	£ 3,082,217
Total PP costs	£ 2,751,684	£ 3,078,795	£ 3,100,164	£ 3,121,533	£ 3,142,901
MP treatment costs	738	826	831	837	843
Market Share	20%	20%	20%	20%	20%
MP treatment costs (£800/pt)	£ 2,361,352	£ 2,642,062	£ 2,660,400	£ 2,678,737	£ 2,697,075
MP monitoring costs (£993.80/pt)	£ 733,347	£ 820,525	£ 826,220	£ 831,915	£ 837,610
Total MP costs	£ 3,094,700	£ 3,462,588	£ 3,486,620	£ 3,510,653	£ 3,534,685
Budget Impact (Current Treatment)	**£ 5,846,384**	**£ 6,541,383**	**£ 6,586,784**	**£ 6,632,185**	**£ 6,677,586**
Overall budget impact	**2012**	**2013**	**2014**	**2015**	**2016**
	£ 22,198,725	**£ 43,737,223**	**£ 44,040,786**	**£ 44,344,348**	**£ 44,647,911**

Table 67. Overall budget impact for the NHS in England and Wales with patient access scheme.

mCRPC post-docetaxel patient population	**2012**	**2013**	**2014**	**2015**	**2016**
	3690	4128	4157	4186	4214
Future Treatment of mCRPC patients post-docetaxel	**2012**	**2013**	**2014**	**2015**	**2016**
AAP treatment costs					
Market Share	27%	46%	46%	46%	46%
Patient numbers	996	1899	1912	1925	1939
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment costs					
Market Share	68%	49%	49%	49%	49%
PP treatment cost (£2.25/mnth/pt)	£ 45,161	£ 36,411	£ 36,664	£ 36,916	£ 37,169
PP monitoring cost (£914.24/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MP treatment costs					
Market Share	5%	5%	5%	5%	5%
MP treatment costs (£800/pt)	£ 590,338	£ 660,516	£ 665,100	£ 669,684	£ 674,269
MP monitoring costs (£993.80/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total MP costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Treatment of mCRPC patients post-docetaxel	**2012**	**2013**	**2014**	**2015**	**2016**
PP treatment costs					
Market Share	80%	80%	80%	80%	80%
PP treatment cost (£2.25/mnth/pt)	£ 53,130	£ 59,446	£ 59,859	£ 60,272	£ 60,684
PP monitoring cost (£914.24/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP costs	£ 2,751,684	£ 3,078,795	£ 3,100,164	£ 3,121,533	£ 3,142,901
MP treatment costs	738	826	831	837	843
Market Share	20%	20%	20%	20%	20%
MP treatment costs (£800/pt)	£ 2,361,352	£ 2,642,062	£ 2,660,400	£ 2,678,737	£ 2,697,075
MP monitoring costs (£993.80/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total MP costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget Impact (Current Treatment)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall budget impact	**2012**	**2013**	**2014**	**2015**	**2016**
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Not applicable.

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