NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Abiraterone acetate (Zytiga®) for the treatment of metastatic castration-resistant prostate cancer in men not previously treated with chemotherapy

February 2014

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List of abbreviations

5-FU	5-fluorouracil
AA	Abiraterone acetate
AAP	Abiraterone acetate plus prednisone/prednisolone
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike's Information Criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
ASCO GU	American Society of Clinical Oncology Genitourinary
AST	Aspartate aminotransferase
AUA	American Urological Association
BIC	Bayesian Information Criterion
b.i.d.	Bis in die (twice a day)
BFI-SF	Brief Fatigue Inventory – Short Form
BNF	British National Formulary
BP	Blood pressure
BPI	Brief pain inventory
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSI	Brief symptom inventory
CAB	Combined androgen blockade
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CLL	Chronic lymphocytic leukaemia
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
CUA	Cost-utility analysis
DAS	Disease activity score
DES	Discrete event simulation
EAU	European Association of Urology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
EQ-5D	EuroQoL five dimensions
ESMO	European Society for Medical Oncology
EWB	Emotional well being
FACIT-Sp	Functional Assessment of Chronic Illness Therapy Scales – Spirituality subscale
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
FRI	Family Relationships Inventory
FWB	Functional well being
G-CSF	Granulocyte colony stimulating factor
HR	Hazard ratio
HRPC	Hormone-resistant prostate cancer
HRQL	Health-related quality of life
HTA	Health technology assessment

HUI	Health Utilities Index
ICER	Incremental cost effectiveness
IDMC	Independent Data Monitoring Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KOL	Key opinion leader
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LFT	Liver function test
LHRH	Luteinising hormone-releasing hormone
LY	Life year
LYG	Life years gained
MBC	Metastatic breast cancer
mCRPC	Metastatic castration-resistant prostate cancer
MFX	Multifraction
Mini MAC	Mini Mental Adjustment to Cancer scale
MRI	Magnetic resonance imaging
MRU	Medical resource utilisation
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reached
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OLS	Ordinary least squares
OS	Overall survival
P	Prednisone
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PCI	Prostate Cancer Index
PCI-SF	Prostate Cancer Index – short form
PCS	Prostate Cancer Scale
PCWG	Prostate Cancer Working Group
PEPPI	Perceived Efficacy in Patient–Physician Interactions
PFS	Progression free survival
Pl	Prednisolone
PORPUS-U(SG)	Patient Oriented Prostate Utility Scale, standard gamble
PORPUS-U(RS)	Patient Oriented Prostate Utility Scale, rating scale
PP	Placebo plus prednisone/prednisolone
PPI	Present pain intensity
PRO	Patient-reported outcomes
PS	Performance status
PSA	Prostate-specific antigen
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PV	Present value
PWB	Physical well being
q.d.	Quaque die (once daily)
QALY	Quality-adjusted life year
QoL	Quality of life
QWB	Quality of well being
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RND	Random number

rPFS	Radiographic progression-free survival
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short Form 36
SFWB	Social/family well being
SFX	Single fraction
SG	Standard gamble
SMC	Scottish Medicines Consortium
SMR	Skeletal morbidity rate
SPC	Summary of product characteristics
SQL	Structured Query Language
SRDB	Systematic Review Database
SRE	Skeletal-related event
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
TNM	Tumour–node – metastasis
TOI	Total Outcome Index
TTO	Time trade off
UCLA	University of California in Los Angeles
UCLA-PCI	University of California in Los Angeles – Prostate Cancer Index
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care 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 10.1 to 10.13) 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', section 11.

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 and treatment options

- Early in its disease course, prostate cancer generally progresses slowly; but as it proceeds to a more advanced and/or metastatic stage, it becomes more rapidly progressive, with high rates of mortality [1] (section 2.1).
- NICE-recommended treatment options include [2] (section 2.5):
  - Localised disease: active surveillance, radical prostatectomy, radical radiotherapy
  - Locally advanced: hormonal therapy (± radiotherapy), radical prostatectomy
  - Metastatic: hormonal therapy, bilateral orchidectomy, chemotherapy, corticosteroids, radioisotopes, bisphosphonates.
- While castration (whether hormonal or surgical) stops testosterone production in the testicles, testosterone production in the adrenal cortex and in the tumour itself persists, resulting in continued tumour growth [3] (section 2.1).
- Prostate tumours that stop responding to hormonal therapy used to be termed 'hormone-refractory' or 'androgen-independent', but it is now recognised that these tumours are still sensitive to hormones produced in locations other than the testicles. The latest NICE guidelines [2] use the term 'hormone-relapsed', while this submission uses 'castration-resistant' prostate cancer (CRPC), to be consistent with the protocol [4] (section 2.1).

UK approved name, brand name, and marketing status

- Approved name: Abiraterone acetate (section 1.1).
- Brand name: Zytiga® (section 1.1).
- Marketing status (section 1.3):
  - Date of Committee for Medicinal Products for Human Use (CHMP) EU approval: 19.11.12.
  - Date of UK marketing authorisation for this indication: 18.12.12.

Principal mechanism of action

- Abiraterone acetate (AA) is converted, in vivo, to abiraterone, which selectively inhibits the enzyme 17α-hydroxylase (CYP17), thus blocking the conversion of pregnenolone and progesterone into testosterone precursors [5] (section 1.2).
- AA blocks androgen biosynthesis in the testes, adrenal glands, and prostatic tumour tissue [6;7] (section 1.2).
- Treatment with AA decreases serum testosterone to undetectable levels when given with luteinising hormone-releasing hormone (LHRH) agonists or after orchiectomy [5] (section 4.1.1).

Formulation, cost, etc.

- Formulation (tablets): AA (250 mg), lactose (189 mg), sodium (6.8 mg), excipients (microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone [K29/K32], colloidal anhydrous silica, sodium laurilsulfate) (summary of product characteristics [SPC] [appendix 1]).
- Strength: 250 mg (section 1.10).
- Pack size: 120 tablets.
- Maximum quantity: no maximum.

- Anticipated frequency of any repeat courses: there is no evidence to support retreatment (section 1.10).
- Acquisition cost (excluding VAT): £2,930 per 30 days without patient access scheme (PAS); [redacted] per 30 days with PAS (section 1.10).

Indications and restrictions

- AA is indicated with prednisone or prednisolone for (section 1.5):
  - The treatment of metastatic CRPC (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated (current submission)
  - The treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen (prior submission).

Recommended course of treatment

- AA 1,000 mg q.d. plus prednisolone 10 mg/day should be taken continuously until clinical assessment shows disease progression (sections 1.10 and 1.14).
- Co-administration of prednisolone suppresses adrenocorticotropic hormone (ACTH) drive, reducing potential adverse events (AEs) associated with AA, such as hypertension, hypokalaemia, and fluid retention [5] (section 2.7).

Comparator

- Of the two possible comparators identified in the NICE scope (best supportive care [BSC] or docetaxel), BSC (e.g. prednisone/prednisolone) is considered to be the appropriate comparator (section 2.7).
- Prednisone/prednisolone has not been found to provide any survival benefit in patients with mCRPC, but corticosteroids do have some anti-cancer activity [8-10] and palliative benefit [11] in some patients (section 2.7).
- As BSC can include corticosteroids, the placebo plus prednisone/prednisolone arm of the COU-AA-302 study can be considered an appropriate comparison population (section 2.7).
- Docetaxel is not a suitable comparator as AA is only indicated in patients in whom 'chemotherapy is not yet clinically indicated' [5] whereas docetaxel is generally reserved for men with symptomatic mCRPC [2;12;13] (section 2.7).
- There is no evidence that starting chemotherapy when the patient is still mildly or asymptomatic is more effective than waiting until the patient is symptomatic [14].

Key clinical evidence

- The ongoing COU-AA-302 trial is a large, multi-centre, randomised, double-blind, placebo-controlled trial. A total of 1,088 asymptomatic or mildly symptomatic men with mCRPC who had failed ADT and not yet received chemotherapy were randomised to AA plus prednisone/prednisolone (AAP) or placebo plus prednisone/prednisolone (PP) (section 6.3.2).
- Patients were classed as asymptomatic or mildly symptomatic from prostate cancer if they had a brief pain inventory (BPI) score for question #3 (worst pain in last 24 hours on a scale of 0–10) of 0–1 (asymptomatic) or 2–3 (mildly symptomatic) (section 6.3.3).

- COU-AA-302 had two co-primary endpoints (radiographic progression-free survival [rPFS] and overall survival [OS]) and a range of secondary endpoints (sections 6.3.2 and 6.3.5).
- Only one analysis was planned for rPFS, which was to occur after approximately 378 events. Independent assessors performed a radiology review in support of the primary analysis for rPFS, which included data up until the clinical cut-off date of 20.12.10. Following the primary rPFS analysis cut-off, subject rPFS data continued to be collected. It was no longer independently reviewed, rather assessed a second time by a central reviewer for exploratory analysis.
- The overall level of significance for the study was 0.05, allocated between the co-primary endpoints of rPFS (0.01) and OS (0.04). Three interim analyses were planned for OS: the first after observation of approximately 116 of the required 773 events (15%), the second after 311 events (40%), and the third after 425 events (55%). A final analysis was planned for after 773 events had occurred.
- The 40% OS data-cut date was 20.12.11. On 27.02.12, the Independent Data Monitoring Committee (IDMC) concluded that subjects in 'Arm X' had a 'highly significant advantage', even though the hazard ratio (HR) for OS had not reached the stringent pre-specified statistical significance level (0.0034). The committee unanimously recommended stopping the study, unblinding, and allowing cross-over. The study was unblinded on 02.04.12. Unmasking of the data revealed that 'Arm X' was AAP (sections 6.3.6 and 6.5.3).
- The data for this submission are from the intent-to-treat (ITT) population at the 55% OS data cut (22.05.12), by which time three PP patients had crossed over to AAP (section 6.3.8). Median follow-up by the time of this analysis was 27.1 months (section 6.5.3.).
- Co-primary endpoint – rPFS:
  - AAP reduced risk of disease progression by 48%
    - rPFS was significantly improved in the AAP vs. PP arm (53.5% vs. 64.9% had rPFS events; median time to event 16.5 vs. 8.2 months; HR 0.52; 95% confidence interval [CI] 0.45, 0.61; p<0.0001) (section 6.5.3).
- Co-primary endpoint – OS:
  - AAP decreased risk of death by 21%
    - OS was improved in the AAP vs. PP arm (36.6% vs. 43.2% deaths; median time to death 35.3 vs. 30.1 months; HR 0.79; 95% CI 0.66, 0.96; p=0.0151) (section 6.5.3).
- Various subgroup analyses showed that the 95% CIs of the HRs for rPFS were all <1; the HRs for OS were all <1, but some of the 95% CIs were >1.
- Secondary endpoints:
  - Time to opiate use for cancer pain: HR 0.71 (95% CI 0.59, 0.85); p=0.0002
  - Time to initiation of cytotoxic chemotherapy: 0.61 (0.51, 0.71); p<0.0001
  - Time to prostate-specific antigen (PSA) progression: 0.50 (0.43, 0.58); p<0.0001
  - Time to deterioration in Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0.83 (0.72, 0.94); p=0.0052
- Other endpoints
  - Various other endpoints (PSA response rate, objective response rate, duration of response, health-related quality of life [HRQL], time to pain progression, and time to analgesic progression) were all in favour of AAP, and these were mostly significant.

- AAP remained safe and well tolerated with longer exposure (section 6.9.2)
  - In the AAP vs. PP arms, there were similar or slightly higher rates of treatment-emergent AEs (TEAEs) (99.3% vs. 97.0%), grade 3/4 TEAEs (49.3% vs. 43.5%), and serious AEs (SAEs) (34.7% vs. 27.0%)
  - The most frequently reported AEs (any grade) were fatigue (AAP 39.7% vs. PP 34.6%), back pain (33.2% vs. 33.1%), arthralgia (29.3% vs. 24.4%), nausea (24.0% vs. 23.0%), and peripheral oedema (26.0% vs. 20.9%)
  - The most frequently reported grade 3/4 AEs were hypertension (4.2% vs. 3.1%), back pain (2.8% vs. 3.9%), alanine aminotransferase increased (5.5% vs. 0.7%), pulmonary embolism (2.0% vs. 2.8%), and hyperglycaemia (2.6% vs. 2.0%)
  - AEs of special interest (events related to mineralocorticoid excess [hypertension, hypokalaemia, and fluid retention], cardiac disorders, and hepatotoxicity) were reported in a higher proportion of patients in the AAP vs. PP group (68.6% vs. 51.3%).

The type of economic evaluation and justification for the approach used

- This submission addresses the cost-effectiveness of AAP vs. BSC (PP) in adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. The BSC arm is based on the PP arm of COU-AA-302, as all patients in this arm received prednisone/prednisolone. Due to their palliative benefit and lack of OS advantage, corticosteroids, such as prednisolone, can be considered a form of BSC for mCRPC (section 7.2.1).
- Statistical and simulation methods were utilised to develop the model which employed a simple discrete event simulation (DES) approach to track patients and their experiences at the individual level. The model adopted a treatment pathway structure, simulating multiple courses of therapy from the start of AAP/BSC (PP) until death (section 7.2.2).
- The pathway structure allows for the tracking of subsequent treatments after discontinuation from AAP and conceptualises the course of mCRPC better than the conventional three-health-state structure of PFS, post-progression, and death (NICE TA259) [15], which oversimplifies the disease clinical pathway after patients discontinue from AAP (section 7.2.3).
- The effectiveness of AAP was estimated based on a series of survival functions: time to AAP/BSC (PP) treatment discontinuation, time to docetaxel start, time from docetaxel start to end, time to post-docetaxel active treatment, and time to death before, during and after docetaxel. These equations ultimately estimated patients' OS and time spent in each treatment phase (section 7.2.2).
- Although the various phases in the treatment pathway outwardly mirror similar descriptions in the naming convention (e.g. BSC [PP], BSC [pre-docetaxel], etc.), each phase actually represents a discrete element of the patient pathway. Importantly, if treatment phases were merged under one depiction, for example, BSC, or any of the identified phases were removed from the treatment pathway, it would be assumed that patients spend zero time in this phase and the model would therefore not be able to replicate the COU-AA-302 trial results or AAP's relative benefit.

Pivotal assumptions underlying the model/analysis

- The base case focuses on the ITT population from the COU-AA-302 study. Data from the 55% data cut-off were used to populate the model (section 7.2.1). Extrapolation beyond trial period is based on data observed in the 302 trial, and censored patients follow the trend/pattern of those who had events.
- Treatment discontinuation from COU-AA-302 was used as a proxy for PFS in the model (section 7.2.5).
- Other sources of data included a patient utility study survey completed by 163 prostate cancer patients (to ascertain utility values for patients in various treatment phases) (section 7.4.3) and a medical resource utilisation survey completed by 103 specialists (section 7.5.4).
- The model takes the perspective of the UK NHS and includes relevant personal social services (section 7.2.6).
- The time horizon in the base case was lifetime to capture the full benefits of treatment (section 7.2.6).

Costs, outcomes and ICERs

- The base-case analysis (including PAS) resulted in an incremental cost-effectiveness ratio (ICER) of £46,722/quality-adjusted life year (QALY) when AAP was compared with BSC (PP) (Table 1 and Table 2) (section 7.7.6).

Table 1: Base-case cost-effectiveness results

	AAP	BSC (PP)
Technology acquisition cost, £	[redacted]	[redacted]
Other costs, £	[redacted]	[redacted]
Total costs, £	[redacted]	[redacted]
Difference in total costs, £	–	26,404
LYG	[redacted]	[redacted]
LYG difference	–	0.62
QALYs	[redacted]	[redacted]
QALY difference	–	0.57
ICER	–	46,722

AAP, abiraterone acetate plus prednisolone; BSC, life years gained; LYG, life year gain; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PP, placebo plus prednisolone.

Table 2: Incremental cost-effectiveness results

Technology (and comparator)	Total cost, £	Total QALYs	Incremental cost, £	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	–	–	–
AAP	[redacted]	[redacted]	26,404	0.57	46,722

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PP, placebo plus prednisolone.

- One-way sensitivity analyses resulted in ICERs of £38,087–60,418/QALY, with post-ADT baseline utility having the greatest impact on results (section 7.7.7).
- Scenario analyses that included PAS resulted in ICERs of £46,114–50,163. The scenario without PAS resulted in an ICER of £[redacted]/QALY.

Subgroup analyses

- Two patient subgroups (BPI #3 0–1 [asymptomatic] and ECOG PS 0 [fully active]) had improved HR (0.74 and 0.77, respectively) for OS compared to the ITT population (HR 0.79) (section 7.9.1).

- The ICERs in these two subgroups were lower than for the overal population.

Table 3: Subgroup analysis results

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY vs. baseline	ICER, £/QALY
BPI #3 0–1								
BSC (PP)	[redacted]	[redacted]	[redacted]					
AAP	[redacted]	[redacted]	[redacted]	29,929	0.75	0.71	–4,657	42,065
ECOG 0								
BSC (PP)	[redacted]	[redacted]	[redacted]					
AAP	[redacted]	[redacted]	[redacted]	27,452	0.62	0.65	–4,453	42,269

BPI, brief pain inventory; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Conclusions

- The key clinical evidence is drawn from a large, multi-centre, randomised, double-blind, placebo-controlled trial (N=1,088) comparing AAP with PP in asymptomatic or mildly symptomatic post-ADT, pre-chemotherapy mCRPC patients.
- In patients with asymptomatic and mildly symptomatic mCRPC without prior chemotherapy, treatment with AAP:
  - Reduced risk of disease progression by 48%
  - Decreased risk of death by 21%
  - Delayed time to opiate use and chemotherapy
  - Improved HRQL and pain measures (FACT-P, BPI-SF)
  - Remained safe and well tolerated with longer exposure.
- Due to a ‘highly significant advantage’ for AAP patients, the trial was stopped prematurely to allow cross-over from PP to AAP despite OS not reaching the stringent prespecified criteria for significance.
- AAP meets an unmet need in asymptomatic or mildly symptomatic mCRPC patients who have failed hormonal therapy, as there are currently no approved or recommended treatments available in the UK.
- It has been estimated that 4,689 men would be eligible for AAP in the current indication in England and Wales in 2014.
- The economic evaluation showed a base-case ICER of £46,722/QALY for AAP vs. BSC (PP).
- Consequently, AAP is equally cost-effective in the post-ADT, pre-chemotherapy setting as in the NICE-approved post-chemotherapy setting (£46,800/QALY [15]).
- Given the existing funding arrangements for AAP in the post-chemotherapy setting, these results present clinicians with the option for earlier use of AAP without having to use docetaxel first. This is key, as patients will be able to benefit from AAP prior to being exposed to the potential toxicities associated with docetaxel at an earlier stage of their disease, when they are fitter and healthier.
- AA is an innovative, efficacious, orally administered, safe, and cost-effective treatment option that could be made available to patients with a serious, life-threatening disease for whom there are currently no other approved or recommended treatment options.

Section A – Decision problem

1 Description of technology under assessment

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

Brand name: Zytiga®.

Approved name: Abiraterone acetate.

Therapeutic class: The World Health Organisation (WHO) International Working Group for Drug Statistics Methodology has established a new Anatomical Therapeutic Chemical code for abiraterone acetate (AA) in L02BX, 'Other hormone antagonists and related agents': L02BX03 abiraterone.

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

AA 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 the testosterone precursors dehydroepiandrosterone and androstenedione [5]. 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 dehydroepiandrosterone and androstenedione, AA blocks androgen biosynthesis at all sites which are important in patients with prostate cancer: the testes, adrenal glands and prostatic tumour tissue [6;7].

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).

Date of Committee for Medicinal Products for Human Use (CHMP) EU approval: 19.11.12.

Date of UK marketing authorisation for this indication: 18.12.12.

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

On page 50 of the European Public Assessment Report (EPAR), the CHMP state: 'After patients become castration resistant and provided that they remain asymptomatic or have mild symptoms, so that chemotherapy is not yet indicated,

different hormonal managements can be used; however, globally there is neither clear consensus nor clear proof of efficacy in terms of survival of available treatments. Such patients who are not in immediate need of chemotherapy may still benefit from alternative therapies. The data derived from study COU-AA-302 are considered to demonstrate a clinically relevant and significant advantage to this group of patients' [16] (appendix 1 EPAR full). Given that these patients did not receive chemotherapy due to their lack of symptoms, the CHMP required that the words 'in whom chemotherapy is not yet clinically indicated' be added to the label wording.

Key conclusions from the EPAR on AA plus prednisone/prednisolone (AAP) are [17] (appendix 1 EPAR summary)

- AAP 'is of benefit when chemotherapy is not yet required'
- The oral administration of AA was considered advantageous
- AA is 'well tolerated and its risks are considered manageable'.

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

AA 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
- The treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated.

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

Study COU-AA-302 was stopped early (between the second and third interim analyses) by the Independent Data Monitoring Committee (IDMC) due to a 'highly significant advantage' for patients on AAP. Although the study is ongoing, three patients on placebo plus prednisone/prednisolone (PP) crossed over to AAP just before the third interim analysis. As more patients will have crossed over by the time of the final analysis, the third interim analysis (presented here) can be considered the most robust dataset to use when considering the clinical benefits of AAP vs. PP.

There are no further studies reporting data in the next 12 months related to the indication under appraisal.

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

N/A.

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

AA has been approved for this indication (post-ADT, pre-chemotherapy) in Argentina, Aruba, Australia, Bolivia, Brazil, Canada, Chile, Costa Rica, Croatia, Curacao, Ecuador, Egypt, El Salvador, European Union, Guatemala, Honduras, Hong Kong, Israel, Jamaica, Kazakhstan, Lebanon, Malaysia, New Zealand, Panama, Paraguay, Philippines, Qatar, Russia, Saudi Arabia, Singapore, Sri Lanka (approval not required), Switzerland, Syria, United States.

AA is also approved for the post-chemotherapy indication in all of the above countries plus Albania, Algeria, Bahrain, Belarus, Colombia, Dominican Republic, India, Jordan, Korea, Kuwait, Mexico, Nicaragua, Peru, Serbia, Thailand, Turkey, United Arab Emirates, Uruguay.

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?

It is anticipated that the Scottish Medicines Consortium (SMC) will appraise AA and that the Department of Health and Social Services and Public Safety in Northern Ireland may review guidance ensuing from NICE regarding the use of AA in the new intended patient population. Janssen anticipates that a submission will be made to the SMC in 04.14 with a decision expected in 07.2014. An All Wales Medicines Strategy Group submission was made in 12.13.

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 4: Unit costs of technology being appraised

Pharmaceutical formulation	Abiraterone acetate
Acquisition cost (excluding VAT)	£2,930 per 30 days without PAS; [redacted] per 30 days with PAS
Method of administration	Oral
Doses	1 g (4 × 250 mg tablets) q.d.
Dosing frequency	Daily until disease progression following clinical assessment
Average length of a course of treatment	Median 13.8 months treatment duration in the RCT [18] (for further information on treatment exposure in the RCT, please see section 6.3.8)
Average cost of a course of treatment	Median treatment cost is £40,434 without PAS; [redacted] with PAS
Anticipated average interval between courses of treatments	AA is administered daily until disease progression (defined by progression of clinical symptoms and/or radiological assessment and/or 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 AAP after clinical disease progression

Dose adjustments	As specified in the SPC [5]: • Pre-existing mild hepatic impairment: no dose adjustment • Pre-existing moderate hepatic impairment: the use of AAP should be cautiously assessed, and the benefit should clearly outweigh the risk • Pre-existing severe hepatic impairment: AA should not be used • Patients who develop hepatotoxicity during treatment: suspension of treatment and dose adjustment may be required. • Mild/moderate renal impairment: no dose adjustment. • Severe renal impairment: no clinical experience in patients with prostate cancer with severe renal impairment. Caution is advised in these patients. • Administration with food significantly increases the absorption of AA. The efficacy and safety of AA given with food have not been established. AA must not be taken with food (see sections 4.2 and 5.2). • Co-administration with medicinal products activated by or metabolised by CYP2D6: caution is advised; dose reduction may be required. • Co-administration with medicinal products activated by or metabolised by CYP2C8: no clinical data. In vitro data show that AA inhibits CYP2C8. • Co-administration with medicinal products that strongly induce CYP3A4: should be avoided.

AA, abiraterone acetate; AAP, abiraterone acetate plus prednisone/prednisolone; PAS, patient access scheme; PSA, prostate-specific antigen; q.d., quaque die (once daily); RCT, randomised controlled trial; SPC, summary of product characteristics; VAT, value added tax.

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.

N/A.

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

During administration of AA, blood pressure, serum potassium, and fluid retention should be monitored monthly [5]. However, patients with a significant risk of congestive heart failure should be monitored every 2 weeks for the first 3 months of treatment, and monthly thereafter. In all patients, serum transaminases should be measured before treatment, every 2 weeks for the first 3 months, and then monthly.

AA must be taken on an empty stomach. No food should be consumed for ≥2 hours before and ≥1 hour after dosing.

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

As detailed in section 1.12, most patients taking AAP will require 2-weekly monitoring for 3 months, then monthly monitoring.

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?

AA is indicated for use with prednisolone or prednisone. The recommended daily dosage of prednisolone or prednisone is 10 mg [5]. Prednisolone is the active metabolite of prednisone; the former is used in the UK, while the latter is used in the US; both drugs have similar effects.

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.

In its earlier, localised, stages, prostate cancer may take a slowly progressing, chronic disease course; however, with time, as prostate cancer proceeds to a more advanced and/or metastatic stage, it becomes more rapidly progressive, with high rates of mortality [1]. Prostate cancer may be asymptomatic, but can be associated with pain and problems with urination. Treatments include active surveillance, local therapy (surgery and radiotherapy), ADT and chemotherapy.

Treatments that reduce testosterone levels (surgical castration or ADT) can result in tumour regression. However, after about 1–2 years the tumour stops responding to such therapy and growth resumes [19-21]. Previously, tumour growth during ADT was thought to occur because the tumour had become ‘hormone-refractory’ or ‘androgen-independent’. However, it is now known that these tumours remain reliant on hormones for growth, but that they become dependent on testosterone arising from sources outside the prostate, such as the adrenal cortex and synthesis within the tumour itself [3]. Conventional castration, whether surgical or medical, does not stop testosterone production in these tissues. Therefore, the latest NICE guidelines [2] use the term ‘hormone-relapsing’. In this submission, we have used the term ‘castration-resistant’ prostate cancer (CRPC) to be consistent with the study protocol [4]. When tumours have spread to other sites in the body, the term metastatic CRPC (mCRPC) has been used.

Prostate cancer progression can be assessed in various ways, such as using prostate-specific antigen (PSA) levels, clinically or radiographically. PSA levels often rise when prostate cancer progresses, and levels can be measured using a simple blood test. Examples of clinical progression would be if a patient needed to start treatment with opiate-based analgesia, or have chemotherapy, radiotherapy, or surgery, or if their Eastern Cooperative Oncology Group (ECOG) performance status (PS) deteriorated. Radiographic progression in the clinical trial setting can be assessed according to the modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria: a definition would be an increase in size of the target lesion(s) of ≥20% in the sum of the longest diameter from the nadir and ≥5 mm absolute increase in the sum of the longest diameter [22]. RECIST criteria are not commonly used for radiographic assessment in daily clinical practice. Rather, a combination of the other techniques is generally used to determine disease progression. In clinical trials, most treatment discontinuations are due to progression, so treatment discontinuation can be used as a proxy for progression.

Pain is a significant component in the progression of mCRPC, defined by the occurrence of disease progression typically with associated rising serum PSA levels despite surgical or medical castration. When a patient becomes symptomatic, common complaints include lower extremity pain, loss of appetite and weight loss, skeletal-related events (SREs; e.g. pathological fracture, cord compression, need for radiation therapy to a bony area), renal failure due to obstruction of the urethra, and

oedema due to obstruction of venous and lymphatic tributaries by nodal metastases [23;24].

In addition to clinical symptoms, prostate cancer is associated with a substantial psychological patient burden; most commonly anxiety and depression [25]. Disease stage is a significant predictor for reduced mental health in these patients [26]. Mental health is further impacted by chemotherapy, with the emergence of depression in particular, but also delayed psychological recovery and mood disturbances [27-30].

The main drivers of reduced health-related quality of life (HRQL) reported by patients with mCRPC are bone pain, fatigue, sexual disturbances and interrupted social relationships [31;32].

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

In 2006, NICE estimated that there were 10,448 men with mCRPC in England and Wales; 0.0195% of the population [33]. Using 2014 population estimates [34], this equates to 11,085 men, and this could be expected to increase to 11,341 in 2018.

Patients eligible for AAP in the post-ADT, pre-chemotherapy setting
Clinical opinion estimates that 40% of the mCRPC population will receive treatment with docetaxel [35], which equates to 4,434 men in 2014. This estimate is aligned with a recent publication, highlighting that the number of men receiving chemotherapy increased from 11% in 2002 to 33% in 2008 within the Thames Valley Cancer Network [36]. The remaining 60% of patients (6,651) were assumed to be chemotherapy-naïve. Of these, it is estimated that 70.5% [37] are asymptomatic or mildly symptomatic. Therefore, in 2014, it is estimated that there will be 4,689 men with mCRPC in whom ADT has failed who are mildly or asymptomatic and who do not yet require chemotherapy (Table 5). Therefore, for the therapeutic indication covered by this submission (AAP post-ADT, pre-chemotherapy), it is estimated that 4,689 men will be eligible in 2014. Table 5 contains the estimated number of patients eligible for AAP in the post-ADT, pre-chemotherapy setting.

Table 5: Estimate of eligible patients

(Proposed) indication	Estimate of the no. of patients in England and Wales eligible for AAP	Data sources
AA is indicated with prednisone or prednisolone for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	4,689	[33-35;37]
AA in combination with prednisone or prednisolone is indicated for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel	2,483	[33-35] and appendix 1

AA, abiraterone acetate; ADT, androgen deprivation therapy; mCRPC, metastatic castration-resistant prostate cancer.

Patients eligible for AAP in the post-chemotherapy setting
Of the 4,434 men estimated to receive docetaxel in 2014, approximately 70% would be eligible for treatment with AAP in the post-chemotherapy setting, which equates to 3,104 men). The 70% accounts for patients who may die on docetaxel treatment, may have rapid deterioration on docetaxel (not suitable for further treatment) or those men in whom AAP may be contraindicated or unsuitable. Four oncologists were consulted to estimate the percentage of patients who would be eligible for AAP following treatment with docetaxel. The responses varied from 55% to 85% (individual responses are collated in appendix 1) and, therefore, we assumed the midpoint of 70% of patients would be eligible for treatment with AAP. This equates to 3,104 patients. As mCRPC patients will be treated earlier in the patient pathway with AAP it is assumed that the number of patients eligible for treatment with AAP in the post-chemotherapy setting will decline as patients who receive AAP in the post-ADT, pre-chemotherapy setting are not eligible for AAP re-treatment post-chemotherapy. It is estimated that there would be approximately 2,483 patients eligible for treatment with AAP in the post-chemotherapy setting in 2014. This is calculated using a phased reduction in the number of eligible patients in ensuing years (please refer to section 8.1 for further details).

Both settings
Therefore a total of 7,172 patients would be eligible for treatment with AAP in both the post-ADT, pre-chemotherapy and post-chemotherapy settings in 2014.

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

Natural estimates of life expectancy in England and Wales for asymptomatic or mildly symptomatic patients with mCRPC for whom chemotherapy is not yet clinically indicated have not been found in the literature. As an alternative, European Association of Urology (EAU) estimates of the mean survival of patients with ‘hormone-refractory’ prostate cancer, now more commonly referred to as CRPC, by clinical criteria (2012) are presented in Table 6 [38]. Among men with mCRPC, estimated survival is around 9–27 months, therefore, the majority of this patient population meet the NICE criteria for short life expectancy (i.e. end-of-life) of 24 months [39]. This is supported by 5-year survival rates of only 26–31% [40-42].

Table 6: Estimated natural survival of patients with hormone-refractory prostate cancer by clinical criteria (Source: Heidenreich et al. [38])

Patient characteristics	Estimated mean survival (months)
Asymptomatic rising PSA	
No metastases	20–36
Minimal metastases	18–27
Extensive metastases	9–12
Symptomatic rising PSA	
Minimal metastases	14–16
Extensive metastases	9–12

PSA, prostate-specific antigen.

These data are also supported by results of chemotherapy trials in mCRPC patients. In a recent meta-analysis of 12 trials of docetaxel-based regimens, median OS was

18–22 months, depending on whether patients received docetaxel alone or in combination with other treatments [43].

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

The most recent NICE guidance documents on the diagnosis and treatment of prostate cancer (clinical guideline 175) have recently become available [2]. There are no recommendations specifically for asymptomatic or mildly symptomatic mCRPC patients for whom chemotherapy is not yet clinically indicated. These guidelines use the term 'hormone-relapsed' prostate cancer, but in this submission we have used the term CRPC as discussed in section 2.1.

When there is biochemical evidence of CRPC, treatment options should be discussed by the urological cancer multi-disciplinary team and, as appropriate, include the specialist opinion of an oncologist and/or palliative care clinician [2]. Since there is no known curative therapy for CRPC, the goals of treatment are to improve survival, HRQL and symptoms. However, CRPC may still respond to agents that work via the androgen receptor (e.g. oestrogens or corticosteroids). Luteinising hormone-releasing hormone (LHRH) analogue therapy is usually continued in patients with CRPC as the androgen receptors on the cancer cells can remain active, and it is a Summary of Product Characteristics (SPC) requirement that such therapy is continued in patients being treated with AA. Third-line hormonal therapy with a corticosteroid such as dexamethasone (0.5 mg daily) after androgen withdrawal and anti-androgen therapy is recommended for men with CRPC.

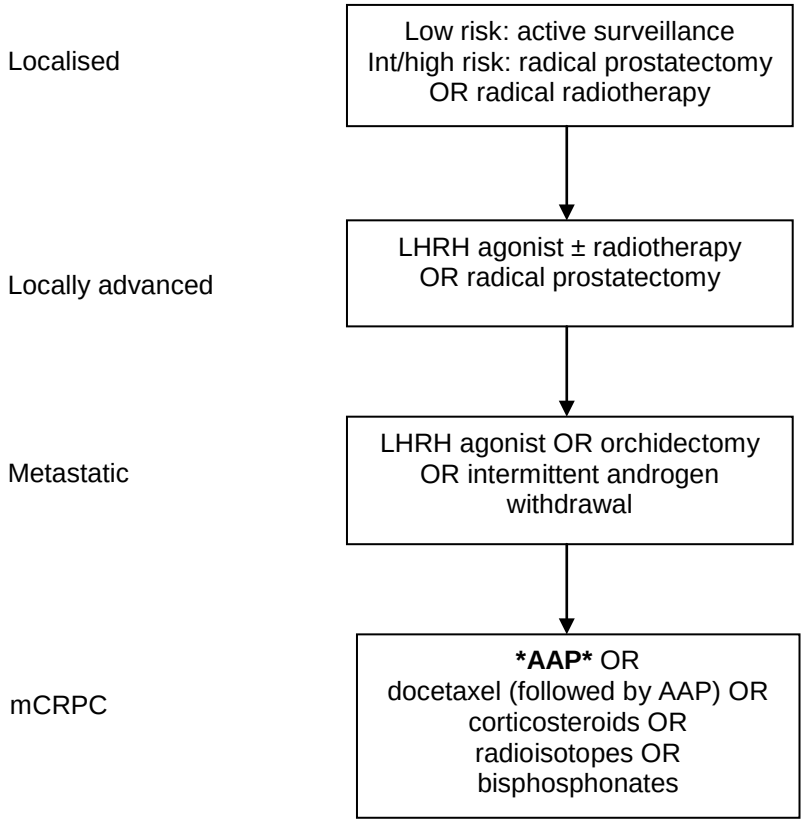
According to NICE guidelines, chemotherapy should usually be reserved for men with symptomatic progression, and the combination of docetaxel + prednisolone can cause substantial side effects [2]. Although these guidelines add that asymptomatic men with metastatic disease and a rapidly rising PSA level may also benefit from chemotherapy, there is no definition of rapidly rising PSA in the guideline. A study by Armstrong et al. [44] found that a PSA doubling time <55 days in conjunction with a baseline PSA ≥114 ng/mL had a significant negative impact on overall survival (OS). Only a minor proportion (approximately 10%) of the population in the COU-AA-302 study met these criteria, so chemotherapy would not be a suitable treatment for the majority of patients. However, it should be noted that PSA doubling time could only be roughly estimated in COU-AA-302.

NICE has also issued guidance for docetaxel [12], cabazitaxel [45] and AAP for patients who have previously received a docetaxel-containing chemotherapy regimen [15].

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

NICE prostate cancer treatment guideline options are outlined in Figure 1 [2]. For men with mCRPC (i.e. after failure of ADT), the options are chemotherapy (if Karnofsky PS ≥60%), corticosteroids, radioisotopes (strontium-89 should be considered for men with painful bone metastases) or bisphosphonates (for pain relief when other treatments have failed). Chemotherapy is usually reserved for men with symptoms or those with rapidly rising PSA levels. The NICE guidelines recognise that the androgen receptors on the cancer cells can remain active in men with hormone-relapsed prostate cancer [2]. The indication for AAP relevant to the submission, in combination with corticosteroids, would provide a treatment option for asymptomatic or mildly symptomatic mCRPC patients in whom chemotherapy is not yet clinically indicated.

Figure 1: Simplified NICE prostate cancer treatment guidelines showing where AAP could be added (shown by *AAP*) [2]



AAP indicates where AAP could fit into the NICE treatment guidelines, as a treatment for patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.
AAP, abiraterone plus prednisolone; LHRH, luteinising hormone-releasing hormone.

Treatment options for mCRPC from the 2013 EAU guidelines on prostate cancer include: oestrogenic compounds, adrenolytic agents, 'novel approaches' (AA or sipuleucel-T), and docetaxel [38]. Chemotherapy is recommended in symptomatic patients, but 'timing is not so clear' in asymptomatic patients. AA is already included in the EAU guidelines as a first-choice option for second-line treatment after relapse

following first-line docetaxel, along with sipuleucel-T. NB Sipuleucel-T is not yet licensed in the UK.

The European Society for Medical Oncology (ESMO) recommendations for mCRPC after first- and second-line treatment (bilateral orchiectomy or LHRH agonist, and anti-androgen) are third-line (e.g. corticosteroid) and possibly fourth-line (e.g. oestrogen or ketoconazole) hormonal therapy. Chemotherapy is recommended for symptomatic patients [13]. AA could potentially fit into these recommendations as third-line therapy with a corticosteroid.

The American Urological Association (AUA) guidelines for men with asymptomatic or minimally symptomatic mCRPC without prior docetaxel chemotherapy recommend AAP, docetaxel or sipuleucel-T [46]. Alternatives for patients who cannot have, or do not want, these therapies are first-generation anti-androgen therapy, ketoconazole plus steroid or observation. They add that, although docetaxel has been shown to improve survival in a study by Tannock et al. [47], this study mainly included symptomatic patients. Also, serious adverse event (SAE) rates were high, which could lead to treatment discontinuation, or patients electing to delay or not receive docetaxel treatment.

The National Comprehensive Cancer Network (NCCN) guidelines for men with mCRPC recommend maintaining castrate testosterone levels and either (1) docetaxel, mitoxantrone, AA, enzalutamide, or clinical trial for symptomatic patients or (2) sipuleucel-T, secondary hormone therapy (including AA), docetaxel, or clinical trial for asymptomatic patients [48]. Importantly, the guidelines add that most asymptomatic patients would not receive chemotherapy, but chemotherapy could be considered for those with signs of rapid progression or hepatic metastases.

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

While NICE [2], EAU [38], ESMO [13], AUA [46] and NCCN [48] guidelines all agree that first- and second-line treatments for patients with metastatic prostate cancer should be androgen withdrawal and anti-androgens, respectively, once the disease has become castration resistant, the guidelines are less clear. Options include corticosteroids [2;13;48], oestrogenic compounds [13;38;48], adrenolytic drugs [38], novel compounds (e.g. enzalutamide [38;48], AA [38;46;48] or sipuleucel-T [46;48]), ketoconazole [13;38;46;48] and chemotherapy [2;13;38;46;48].

There is a clear consensus that patients with symptomatic mCRPC should be given chemotherapy (although only for those with a Karnofsky score ≥60% according to NICE [2]). However, in asymptomatic patients, recommendations are unclear, and include: that men with a ‘rapidly rising’ PSA may benefit from chemotherapy, but that ‘a rising PSA alone should not necessarily prompt an immediate change in treatment’ (NICE [2]); that each patient should be ‘discussed individually’ (EAU [38]); no recommendation (ESMO [13]); administration of AAP, docetaxel or sipuleucel-T (AUA [46]); or administration of sipuleucel-T, secondary hormone therapy (including AA), docetaxel or clinical trial (NCCN [48]). Most of the non-chemotherapeutic treatment options listed above have not shown any survival benefit. However, chemotherapy for patients with mCRPC is associated with a risk of grade 3/4

toxicities [49-51], potentially making the risks of treatment outweigh the benefits in patients with no or mild symptoms. Patients may also elect not to receive docetaxel due to SAEs [46]. Furthermore, the trial by Tannock et al. [47] included mainly symptomatic patients, so efficacy in asymptomatic patients is less well established. A novel immunotherapy treatment, sipuleucel-T, which requires development of patient-specific infusions, offers a survival benefit but is not yet available in the UK. It is currently being appraised by NICE.

Therefore, there is a compelling need for a rigorously evaluated, non-chemotherapeutic treatment that prolongs the time during which patients have no or minimal symptoms and increases survival for men with mCRPC.

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

The NICE scope identified two possible comparators: best supportive care (BSC; this may include corticosteroids, radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and mitoxantrone with or without corticosteroids) or docetaxel. Of these, BSC is the appropriate comparator for AA. As BSC can include corticosteroids, the placebo arm of the COU-AA-302 study can be considered an appropriate comparison population, as patients in the placebo arm all received corticosteroids as part of supportive care.

Although a survival benefit for single-agent prednisone/prednisolone in mCRPC has not been shown, corticosteroids do have some anti-cancer activity (a ≥50% PSA decline is seen in ~20% of patients) [8-10] and palliative benefit (relief of pain) in some patients with advanced prostate cancer [11]. There is no known relationship between the dose/regimen of prednisone or prednisolone and observed anti-tumour activity in mCRPC. Co-administration of a corticosteroid (prednisone or prednisolone) with AA also suppresses ACTH drive, resulting in a reduction in the incidence and severity of potential adverse events (AEs) associated with AA, such as hypertension, hypokalaemia and fluid retention [5]. Further supportive care agents included in study COU-AA-302 were LHRH agonists, conventional multivitamins, selenium and soy supplements, ‘stress dose’ corticosteroids, transfusions or haematopoietic growth factors.

Docetaxel was identified as a potential comparator of interest in the NICE scope for this appraisal. Whilst both AAP and docetaxel are indicated for the treatment of mCRPC for adult men following ADT failure, AAP is indicated for the treatment of those in whom chemotherapy is not yet clinically indicated, the asymptomatic or mildly symptomatic patient [5;52]. The European Medicines Agency (EMA)’s benefit–risk assessment concluded that ‘data derived from study COU-AA-302 are considered to demonstrate a clinically relevant benefit to patients who require additional therapeutic options’ [16]. Patients who are not in immediate need of chemotherapy have the potential to benefit from alternative treatments such as AAP and the ‘data derived from study COU-AA-302 are considered to demonstrate a clinically relevant and significant advantage to this group of patients’ [16]. As AAP is indicated in a patient population for whom chemotherapy is not yet clinically indicated, this submission does not include docetaxel as a comparator.

In alignment with the scope for this appraisal, a systematic review of the literature was undertaken to identify any docetaxel studies that were conducted in similar patient populations to the COU-AA-302 study. The evidence identified to compare docetaxel with AAP is very limited. No head-to-head studies comparing AAP with docetaxel were identified and the systematic review revealed that most studies involving docetaxel were designed to explore the clinical benefit of new experimental interventions added onto a docetaxel regimen. The one study that did compare docetaxel with prednisolone (TIPC) [53] was a small, phase II study in a more symptomatic patient population than the COU-AA-302 population, however the different populations and study methodologies prevented any indirect comparison of key outcomes between AAP and docetaxel. Evidence to assess the comparative clinical benefit of docetaxel in a population equivalent to that of AA's licence (an asymptomatic or mildly symptomatic patient population in whom chemotherapy is not yet clinically indicated) is therefore limited.

UK clinical practice is currently aligned with NICE guidelines [2], whereby docetaxel is usually reserved for more symptomatic patients. Docetaxel is generally not used in asymptomatic patients. ESMO guidelines only recommend docetaxel in symptomatic mCRPC patients [13], while EAU guidelines [38] state the timing of its use in asymptomatic patients is unclear, and NICE guidelines [2] state that chemotherapy is usually used for symptomatic patients (although asymptomatic men with rapidly rising PSA may also benefit).

There is no evidence that starting chemotherapy when the patient is still asymptomatic or mildly symptomatic is more effective than waiting until the patient is more highly symptomatic. An updated survival analysis of the docetaxel registration study TAX327 analysed various subgroups (including patients with/without 'substantial' pain, with high/low Karnofsky PS and with differing Functional Assessment of Cancer Therapy – Prostate [FACT-P] scores) but concluded that the analysis did not address whether docetaxel should be used in patients with minimal symptoms or whether it should be deferred until patients have more symptoms [14].

Clinical opinion from Simon Chowdhury, a Consultant Medical Oncologist in England (sought for the purposes of this submission), was that prednisolone was the most appropriate comparator for AAP, and that prednisolone may be considered a suitable proxy for BSC [54]. NICE prostate cancer clinical guidelines specify that corticosteroids should be offered as third-line therapy for mCRPC after ADT [2], and a health economic advisory board conducted in London (December 2012 [55]) also concluded that this comparator was the most appropriate to use in the UK.

In conclusion, based on the lack of available comparative evidence in an aligned patient population and on current UK clinical practice, docetaxel was not considered to be a comparator of interest for this submission. Therefore, BSC (corticosteroid) should be considered the most appropriate comparator for AAP in this patient population.

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

In a small number of cases, AA may cause hypertension, hypokalaemia or fluid retention [5], however co-administration of prednisolone reduces the frequency and severity of these AEs. If these AEs do occur, 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 [56].

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

As AAP is self-administered orally in the patient's home, there are no anticipated costs due to location of care, staff or administration.

With administration of AAP, blood pressure, serum potassium and fluid retention should be monitored before treatment and at least monthly thereafter [5]. Patients with a significant risk of congestive heart failure (exemplified in the SPC for AA [5] as those with a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease) should be monitored every 2 weeks for the first 3 months of treatment by measuring blood pressure and serum potassium levels and checking for signs of oedema. To monitor for hepatotoxicity, serum transaminases should be measured in all patients before treatment with AA and every 2 weeks for the first 3 months, and then monthly. Monitoring would be carried out as an outpatient visit to an oncology clinic [57]. After the initial more frequent monitoring needs to determine hepatotoxicity and potentially congestive heart failure parameters, the frequency of follow-up visits (monthly) would be similar to that of other treatment options in this patient population [57].

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

No.

3 Equality

3.1 Identification of equality issues

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

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

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

No issues relating to equity or equality have been identified.

3.1.2 How has the analysis addressed these issues?

N/A.

4 Innovation

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

AA is a novel drug for the treatment of prostate cancer that was discovered and initially developed in the UK. It can be considered innovative and offers a 'step-change' in the treatment of asymptomatic and mildly symptomatic patients with mCRPC after failure of hormonal therapy in whom chemotherapy is not yet indicated for the following reasons:

1. Abiraterone has a unique mechanism of action. By inhibiting the production of both dehydroepiandrosterone and androstenedione, abiraterone blocks androgen biosynthesis at all sites in the body, including the testes, adrenal glands and prostatic tumour. Treatment with AA therefore decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists or after orchiectomy [5].
2. AA is the first treatment to be specifically evaluated in, and licensed for, this stage of the disease (i.e. after failure of ADT but before chemotherapy), fulfilling an important and previously unmet clinical need.
3. There are currently no treatment options that have been shown to delay progression and improve survival in this patient population in appropriately designed clinical trials. These patients are resistant to conventional hormonal therapy, while chemotherapy with docetaxel is currently recommended for patients who are at a later stage of mCRPC who have more severe symptoms, specifically substantial pain [47] and visceral organ metastasis.
4. The most important benefits of AA are extension to life (OS improvement of 5.2 months in men with life expectancy <24 months, making AA a life-extending end-of-life treatment according to NICE guidelines [39]), improved HRQL (less pain and improved mental and physical health), and delayed times to initiation of chemotherapy, disease progression, the use of opiates for cancer pain and deterioration of PS. AA has been shown to be well tolerated. AEs are generally straightforward to manage and are comparable to those associated with conventional hormonal treatment.
5. AA meets the needs of patients with a serious life-threatening disease who have no other evidence-based treatment option at this stage of their illness. This delays the time period before patients progress and would then typically receive treatment with chemotherapy, which is associated with a significant risk of grade 3/4 toxicities [49-51].

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

AAP is currently being tested in a pilot homecare study [58], in which a homecare nurse visits the patient in their home every 2 weeks for 3 months, then monthly, to take blood samples and other observations. The patient's drugs (AA and

corticosteroids) are also delivered to their home for self-administration. Most patients involved in this study felt that this approach is less stressful than treatment in hospital, and interferes less with family and social activities. The majority were extremely satisfied. It also saves patients time and costs associated with attending hospital, increases consultant productivity, and releases clinic slots for other patients. These benefits are unlikely to be quantified in the quality-adjusted life year (QALY) calculation.

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

The judgements are derived from the following sources:

- Mechanism of action: Janssen-Cilag Ltd. Zytiga SPC: Electronic Medicines Compendium. 2013 [5]
- Safety and efficacy of AA: COU-AA-302 study report, abstract and published paper [18;59;60]
- EAU and ESMO guidelines: Horwich et al. [13] , Heidenreich et al. [38]
- Information regarding a lack of treatment options: Heidenreich et al. [49], Sonpavde et al. [50]
- Patient satisfaction with homecare for AA [58].

5 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 mCRPC who have not received prior cytotoxic chemotherapy or biologic therapy	Men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	AA received a marketing authorisation for an indication in this patient population from the EMA in December 2012
Intervention	AA in combination with prednisolone	As per scope	–
Comparator(s)	Docetaxel BSC (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and mitoxantrone with or without steroids or steroids alone)	The appropriate comparator for AAP is BSC. In COU-AA-302, AAP was compared with PP; supportive care was permitted in both arms during the treatment phase as per institutional guidelines. The following agents were permitted: LHRH agonists, multivitamins, selenium and soy supplements, 'stress dose' glucocorticoids, transfusions, haematopoietic growth factors	Due to their palliative benefit (pain relief [11]), prednisone or prednisolone can be considered a form of BSC. The co-administration of one of these agents with AA is also necessary to suppress ACTH drive to reduce the incidence and severity of potential AEs such as hypertension, hypokalaemia and fluid retention [5] Docetaxel is not an appropriate comparator for AA in the intended patient population for the reasons discussed in section 2.7; briefly: • AAP is licensed for men with mCRPC who are mildly or asymptomatic while docetaxel is generally reserved for symptomatic patients [2;5;13;52] • UK clinical practice is currently aligned with NICE clinical guideline 175 [2], whereby docetaxel is usually reserved for the more symptomatic patient • AAP demonstrates a clinically relevant benefit and significant advantage to patients who require additional therapeutic options [16] but are not in immediate need of chemotherapy • There is a lack of clinical evidence supporting the use of docetaxel in a truly asymptomatic or mildly symptomatic patient population [14] • There is no evidence that starting chemotherapy when the patient is still asymptomatic or mildly symptomatic is more effective than waiting until the patient is more highly symptomatic
Outcomes	• OS • PFS • Response rate • PSA response	The following outcomes were prespecified in the protocol: • Co-primary: OS, rPFS • Secondary: times to: opiate	Additional endpoints were included in the COU-AA-302 study

	• AEs of treatment • HRQL	use, chemotherapy, ECOG PS deterioration, PSA progression • Other: objective response rate, PSA response rate, duration of response, HRQL, time to pain progression, time to analgesic progression • Safety: AEs, SAEs, laboratory tests	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. 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.	As per scope	–
Subgroups to be considered	BPI 0–1	BPI 0–1 ECOG 0	BPI 0–1 as per scope; ECOG 0 was also felt to be clinicallyrelevant
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation	As per scope	–

AA, abiraterone acetate; AAP, abiraterone acetate plus prednisone/prednisolone; ACTH, adrenocorticotropic hormone; ADT, androgen deprivation therapy; AE, adverse event; BSC, best supportive care; BPI, brief pain inventory; CHMP, Committee for Medicinal Products for Human Use; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; HRQL, health-related quality of life; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; OS, overall survival; PFS, progression-free survival; PS, performance status; PSA, prostate-specific antigen; QALY, quality-adjusted life year; rPFS, radiographic progression-free survival; SAE, serious adverse event.

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A full systematic review has previously been conducted to evaluate the clinical efficacy, safety and tolerability of AA in mCRPC patients. This review was used in a previous NICE STA) submission (NICE TA259), but focused on a subset of studies in patients with mCRPC who had disease progression despite treatment with docetaxel [61]. For the current submission, an update to the systematic review was conducted. In this update, the focus was on those studies specific to the indication stated within the decision problem of this submission: patients with mCRPC who are asymptomatic or mildly symptomatic (defined as ECOG 0–1 and brief pain inventory – short form [BPI-SF] score of 0–1 [asymptomatic] or 2–3 [mildly symptomatic]) after failure of ADT in whom chemotherapy is not yet clinically indicated.

Searches of electronic databases and relevant conference proceedings were updated to 09.13. To ensure consistency and avoid introducing bias into the review update, no amendments to the review protocol or the search strategy were made. Data sources for the systematic review are presented in Table 7.

Table 7: Summary of data sources for the systematic review

Search strategy component	Sources	Date limits
Bibliographic database searches	MEDLINE® and MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	Database start to 02.09.13
Conference proceedings	ASCO annual meeting	2006–2013
	ASCO GU symposium	2006–2013
	AUA	2006–2013
	EAU	2006–2013
	ESMO	2006–2012a

[a]At the time of the search, ESMO 2013 had not yet taken place.
ASCO, American Society of Clinical Oncology; ASCO GU, American Society of Clinical Oncology Genitourinary Cancers; AUA, American Urological Association; EAU, European Association of Urology; ESMO, European Society for Medical Oncology.

To be included in the review, trials had to meet pre-defined eligibility criteria specified in the systematic review protocol; only studies published in English were included (the full inclusion criteria are listed in section 6.2).

Abstracts of citations identified through the searches were initially reviewed for inclusion based on title and abstract alone. Full-text copies of studies that potentially met the inclusion criteria were obtained. In instances where it was not possible to determine whether studies met the inclusion criteria based on their abstracts alone, full texts were obtained for further assessment. Full-text papers were screened and included or excluded accordingly.

To avoid falsely excluding any studies in the population relevant to the current decision problem, studies were categorised as investigating chemotherapy-naive, post-chemotherapy, or mixed populations once the full publication had been reviewed. Studies that included chemotherapy-naive patients or a mixed population with a subgroup analysis of chemotherapy-naive patients, and met the eligibility criteria following full-text screening, were included to form the evidence base of the submission.

Data from the studies were extracted by two analysts and any discrepancies were reconciled by a third independent analyst. A critical appraisal of the study, using the assessment criteria recommended in the NICE manufacturer's template, was also conducted in a similar manner.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The updated review for this submission utilised a broad set of inclusion criteria (Table 8), and included all studies in mCRPC. This was to ensure consistency between the original review and this update. For the purposes of this submission, focus was given to studies that included post-ADT, pre-chemotherapy patients or a mixed population with a subgroup analysis of post-ADT, pre-chemotherapy patients. These studies match the population stated in the decision problem for this submission more closely, although no restriction on inclusion was made based on whether the patients in the study had received prior ADT.

Table 8: Inclusion and exclusion criteria used in the systematic review

	Clinical effectiveness	Rationale
Inclusion criteria	**Population** Age: Adults (≥18 years) Gender: Any Race: Any Disease/disease stage: mCRPC	• The patient population included in this review was a broader population of patients with mCRPC. The subset of studies including post-ADT, pre-chemotherapy patients was identified prior to data extraction • In line with marketing approval and the decision problem of this submission studies including children or adolescents were excluded
	Interventions **Standard of care (England and Wales):** docetaxel, mitoxantrone, estramustine, cyclophosphamide, 5-fluorouracil, doxorubicin, carboplatin, etoposide, paclitaxel, vinorelbine, vinblastine, dexamethasone, hydrocortisone, prednisone, strontium, zoledronate **Investigational interventions:** abiraterone, sipuleucel-T, MDV3100, bevacizumab, atrasentan, dasatinib, ZD4054, patupilone, AS1404, ipilimumab, sunitinib, IMC-A12, aflibercept, cabazitaxel (XRP6258), JM216, alpharadin	• The list covers common interventions used for the treatment of mCRPC in the UK
	Comparator Another included intervention, best supportive care (includes radiotherapy, corticosteroids, oxygen, analgesics), or placebo	• A wide range of chemotherapy-based combinations are being investigated besides BSC. These comparators were selected to enable the inclusion of all relevant citations • Exclusion of studies based on the comparator used was applicable only for RCTs. RCTs have high internal validity and are considered to represent the gold standard of clinical evidence • Observational studies and non-RCTs were included regardless of the comparator treatment evaluated, given the external validity of these type of studies
	Study design RCTs Non-RCTs Single-arm studies Dose-finding studies Observational studies, including: • Cohort studies (prospective and retrospective) • Case-control studies • Cross-sectional study/survey • Analysis of database/clinical records	• 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 broad patient populations and reflect real world evidence and thus have external validity
	Language restrictions English only	• The restriction would not limit results substantially due to publication availability in the English language and within the NICE scope of the current submission
	Publication timeframe **Original review:** All publications up to and including the cut-off date of 30.05.11 All conference proceedings from	• Searches of conference proceedings were limited to the previous 7 years as studies presented at conferences are usually published in journals within 6 years (conference data older than 7 years which

	01.01.06 until the cut-off date of 08.06.11 **Review update:** All publications from 31.05.11 to 02.09.13 All conference proceedings from 08.06.11 to 02.09.13	have not been published in journals after this duration are unlikely to be useful for the purposes of this review)
	Outcomes of interest Studies should report at least one of the following outcomes of interest: • OS • PFS (including both symptomatic and radiographic PFS) • Time to progression (according to PSA and RECIST criteria) • WHO PS improvement • Overall mortality • Response rate (according to prostate-specific antigen and RECIST criteria) • Duration of response • Prostate-specific antigen measurements • EORTC QLQC30 • EQ-5D • FACT-P score and its subscale • BPI score • PPI • Bone pain • Pain response • Time to pain progression • Time to opiate use • VAS pain score • Analgesic score • Time to first SRE • SMR • Vertebral fractures • Non-vertebral fractures • AEs • Withdrawals and discontinuations	• Studies that did 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 and include those outcomes specified in the decision problem.
Exclusion criteria	**Population** Disease: Prostate cancer other than mCRPC, Secondary prostate cancer **No subgroup analysis** 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 **Study design** Case studies, case series, case reports, and studies in Phase I	• Case-series and case-reports were not included in the review as they are generally smaller, non-comparative studies that have a higher risk of bias • Phase I studies were excluded as they aim to establish the safety profile rather than clinical effectiveness

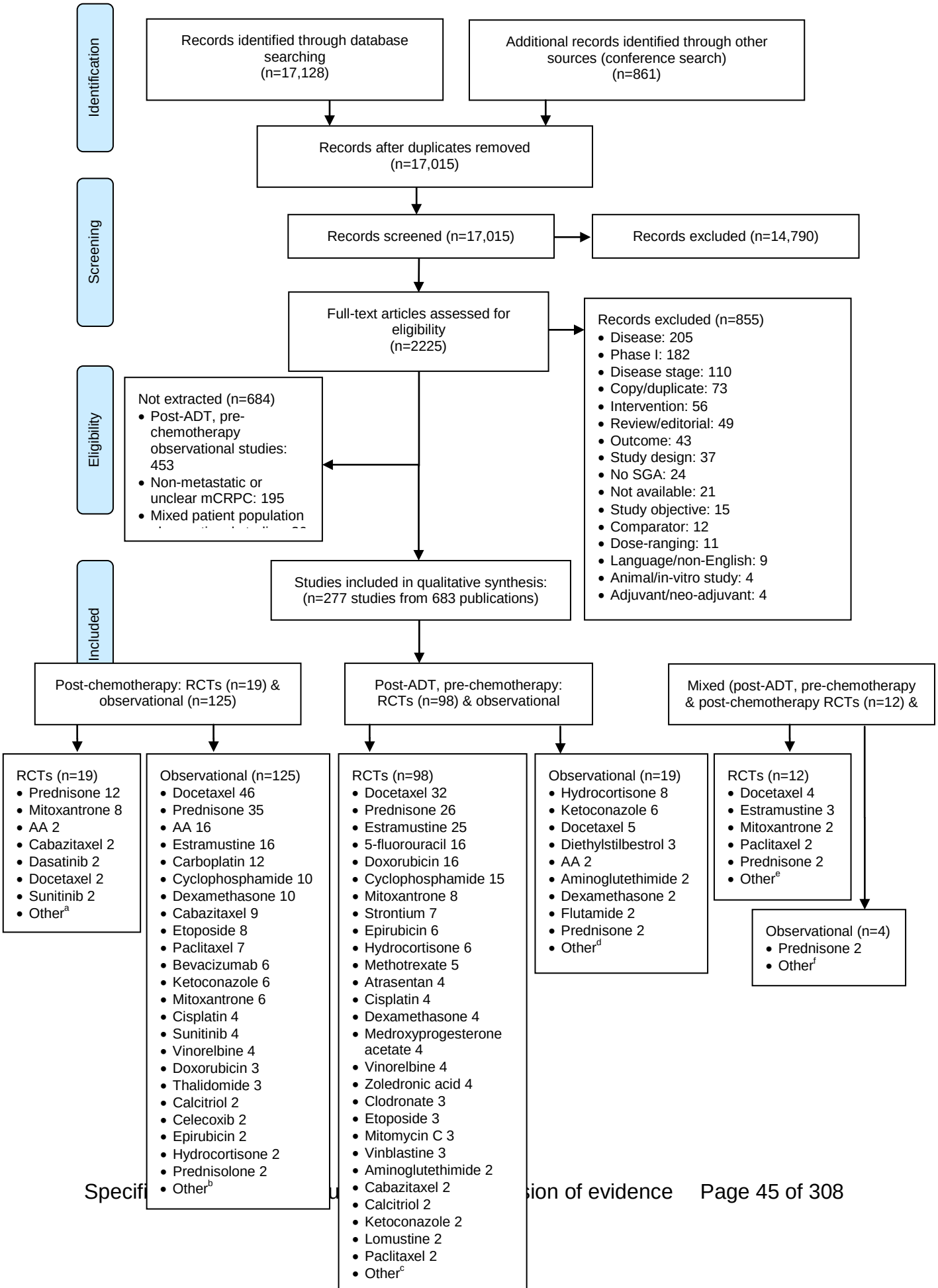
ADT, androgen deprivation therapy; BPI, brief pain inventory; BSC, best supportive care; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQoL Five Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; mCRPC, metastatic castration-resistant prostate cancer; NICE, National Institute for Health and Clinical Excellence; PFS, progression-free survival; PPI, present pain intensity; PS, performance status; PSA, prostate-specific antigen; RCT, randomised controlled trial; RECIST, Response

Evaluation Criteria In Solid Tumors; SMR, skeletal morbidity rate; SRE, skeletal-related event; VAS, visual analogue scale.

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

The systematic review in this submission (the original systematic review plus the update review) identified a total of 277 studies that met the broader inclusion criteria of patients with mCRPC (Figure 2). Of these, 117 studies (98 randomised controlled trials [RCTs] and 19 non-RCTs) were in post-ADT, pre-chemotherapy mCRPC patients. A further 16 studies included a mixed population of mCRPC of both post-ADT, pre-chemotherapy and post-chemotherapy patients without reporting data specific to the relevant subgroup and were therefore excluded from further analysis.

Figure 2: Consort flow of systematic review to identify AA and comparator clinical trials and non-RCT studies



[a]One study for each of: capecitabine, carboplatin, cediranib, cetuximab, custirsen, cyclophosphamide, dexamethasone, enzalutamide, etoposide, everolimus, irofulven, ixabepilone, rilotumumab, satraplatin, siltuximab, thalidomide, vinorelbine, zibotentan.
[b]One study for each of: 5-flurouracil, bortezomib, capecitabine, cetuximab, dasatinib, diethylstilbestrol, doxifluridine, enoxaparine, enzalutamide, estradiol, etoricoxib, gefitinib, gemcitabine, GM-CSF, ipilimumab, ixabepilone, lanreotide, lenalidomide, methotrexate, oxaliplatin, patupilone, pioglitazone, pirarubicin, samarium153, satraplatin, tegafur-uracil, temsirolimus, tesmilifene, treosulfan, triptorelin, vinblastine, vincristine, zoledronic acid.
[c]One study for each of: AA, aflibercept, alpha-interferon, alpharadin, androgen ablation, AT-101, bevacizumab, cediranib, chlorambucil, dacarbazine, dasatinib, diethylstilbestrol, doxercalciferol, ellagic acid, fluoxymesterone, gefitinib, hydroxyurea, interferon, ixabepilone, lanreotide, lenalidomide, LHRH analogue, melphalan, oblimersen, OGX-011, patupilone, peplomycin, peptide vaccine, prednimustine, prednisolone, procarbazine, retinoic acid, risedronate, semustine, SGN-15, sipuleucel-T, streptozotocin, SU5416, suramin, MVA-5T4, vadimezan, vandetanib, VT122, zibotentan.
[d]One study for each of: ADT, ascorbic acid, cisplatin, cyclophosphamide, doxorubicin, epirubicin, estramustine, GM-CSF, mitoxantrone, sipuleucel-T, tegafur-uracil.
[e]One study for each of: 5-fluorouracil, alpharadin, carboplatin, cisplatin, diethylstilbestrol, doxorubicin, imatinib, oxaliplatin, personalized peptide vaccination, sipuleucel-T, strontium, zibotentan.
[f]One study for each of: cyclophosphamide, dasatinib, docetaxel, ketoconazole, LHRH agonist.
AA, abiraterone acetate; ADT, androgen deprivation therapy; GM-CSF, granulocyte macrophage-colony stimulating factor; LHRH, luteinising hormone-releasing hormone; RCT, randomised controlled trial; SGA, subgroup analysis.

The systematic review identified three AA studies in the post-ADT, pre-chemotherapy subset: one RCT and two single arm studies:

- RCT; COU-AA-302, reference details in Table 9; study described in section 6.3
- Two single arm studies; Attard 2009 and Ryan 2011 [62;63], described in section 6.2.7.

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

The data presented in this section are from a single, pivotal RCT comparing AAP with PP (prednisone in the US or prednisolone in Europe), the COU-AA-302 study. The data for this study are derived from both published and unpublished sources at three different time points, as listed in Table 9.

One final and three interim analyses were pre-planned for this study and are described in the study protocol. The interim analyses were planned to coincide with survival events as detailed in section 6.3.6. As such, data from COU-AA-302 are available from various published and unpublished sources at different time points reflecting the timing of the pre-planned interim analyses (Table 9).

The most recently available data from COU-AA-302, which is an ongoing study, are from the third interim analysis. These data are primarily as yet unpublished, with the exception of those sections which have been presented in a review paper [64] and various conference abstracts (see Table 9). A full paper is currently in preparation. The data source for this submission is predominantly derived from an updated clinical study report (CSR) and must be considered commercial in confidence.

Table 9: Data sources for the pivotal RCT, COU-AA-302

COU-AA-302 analysis point	Cut-off date for the analysis	Data availability	Data source
First interim analysis	20.12.10	Unpublished	Clinical study report [65]
Second interim analysis	20.12.11	Published	Ryan et al. 2013 [59] Review article [64] Patient-reported outcomes [66] Conference abstracts (ASCO, ESMO) [67;68]
		Unpublished	Clinical study report [65]
Third interim analysis	22.05.12	Unpublished	Updated clinical study report [18]
		Published	Review article [64] Conference abstracts (ASCO, ASCO GU) [60;69-74]
Final analysis	N/A	N/A	N/A

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

Complete list of relevant RCTs

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

Table 10: List of relevant RCTs

Study	Intervention	Comparator	Population	Study refs.
COU-AA-302	AA (1 g q.d.) + prednisone/ prednisolone (5 mg b.i.d.)	Placebo + prednisone/ prednisolone (5 mg b.i.d.)	Asymptomatic or mildly symptomatic patients with an ECOG PS score of 0 or 1 with mCRPC after failure of ADT in whom chemotherapy was not yet clinically indicated	2nd interim analysis: • Original CSR COU-AA-302 [65] • Ryan et al. 2013 [59] • ASCO and ESMO abstracts [67;68] 3rd interim analysis • Updated CSR COU-AA-302 [18] • ASCO and ASCO GU abstracts [60;69-74]

AA, abiraterone acetate; ASCO, American Society of Clinical Oncology; ASCO GU, American Society of Clinical Oncology Genitourinary Cancers; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society for Medical Oncology; mCRPC, metastatic castration-resistant prostate cancer; PS, performance status.

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

As stated in the Statement of the Decision Problem (section 5), the appropriate comparator for AAP is BSC.

COU-AA-302 is a Phase III study that compares AAP vs. PP in patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. Permissible supportive care agents included LHRH agonists, conventional multivitamins, selenium and soy supplements, ‘stress dose’ glucocorticoids, transfusions, or haematopoietic growth factors.

In prospective Phase III clinical trials, single-agent prednisolone has demonstrated palliative benefits in mCRPC populations [9;10]. Significant improvements in pain, qualify of life and fatigue were also reported. NICE guidelines also recommend the use of corticosteroids in this patient population [2]. Therefore, the PP arm of the COU-AA-302 study is considered to be representative of BSC in the UK and provides evidence directly relating to the intervention and appropriate comparator as outlined in the decision problem.

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

No other head-to-head RCTs involving AAP in the population relevant to the decision problem were identified and therefore no studies were excluded.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

Two non-RCTs were identified by the systematic review described in section 6.1. A summary of these studies is provided in Table 11.

Table 11: List of relevant non-RCTs

Study no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
COU-AA-001 (and COU-AA-001 EXT)	AA (≤2,000 mg q.d.)	Patients with chemotherapy-naive CRPC (>90% of whom had mCRPC)	Determine the maximum tolerated dose and evaluate the safety, tolerability, and activity of AA in patients with chemotherapy-naïve CRPC	Attard et al., 2009 [62]	This Phase 1/2, single-arm, open-label study provides supportive data demonstrating efficacy and tolerability of AA. PSA response (≥50% decline) was observed in 67% of patients

COU-AA-002	AA (1,000 mg q.d.) plus prednisone (5 mg b.i.d.)	Patients with chemotherapy-naive mCRPC	Determine the maximum tolerated dose of AA in men with chemotherapy-naïve mCRPC	[63;75-81]	This Phase 1/2 open-label dose-escalation study provides supportive data demonstrating efficacy and tolerability of AA. PSA response (≥50% decline) was observed in 67% of patients

AA, abiraterone acetate; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; q.d., quaque die (once daily); RCT, randomised controlled trial.

6.3 Summary of methodology of relevant RCTs

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

Primary data for this submission were derived from the third interim analysis of the COU-AA-302 study. This analysis has not yet been fully published, and therefore data presented in this submission are sourced from the CSR [18] and American Society of Clinical Oncology (ASCO) Genitourinary (GU) 2013 conference [60;69-74].

The methodology of this study, along with results of the second interim analysis, is available in the public domain (as reported in a manuscript [59] and supplemented by abstracts presented at the ASCO and ESMO 2012 conferences [67;68]). Additional details relating to the methodology of the study have been added to this document from the unpublished first/second interim analysis CSR [65].

Methods

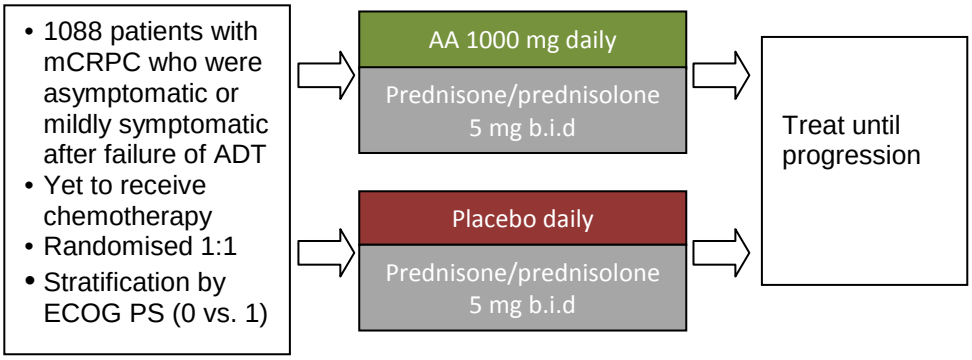
6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The COU-AA-302 study is a Phase III, multinational, multicenter, randomised, double-blind, placebo-controlled study. The rationale was to compare the use of AAP to PP in patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy was not yet clinically indicated (Table 12). Patients included in this study were medically or surgically castrated males who had shown tumour progression and were mildly symptomatic or asymptomatic. A total of

1,088 patients were enrolled from 151 global study sites; 12 sites (9.0% of patients) were from the UK.

As described in the study protocol, one final and three interim analyses were pre-planned during the course of the study to coincide with key cut-offs based on the number of survival events observed (detailed in section 6.3.6). An external IDMC monitored and advised on the interim safety and efficacy aspects of the study and the relevance of new external information as specified in the IDMC charter. Key efficacy and safety (e.g. SAEs) data were provided to the IDMC with treatment groups randomly identified as either 'X' or 'Y'. Treatment group identification could only be obtained from the Independent Biostatistician if the IDMC determined that un-blinding was necessary to decide whether the study should be stopped early for safety or efficacy reasons.

Table 12: Summary of the methodology of the COU-AA-302 study

Variable	COU-AA-302
Location	151 sites worldwide in Australia, Belgium, Canada, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, the UK, and the US (12 study sites and 9.0% of patients were from the UK)
Design	Phase III, randomised, double-blind, placebo-controlled study of AAP versus PP (1:1)
Patient population	Asymptomatic or mildly symptomatic patients with mCRPC after failure of ADT in whom chemotherapy was not yet clinically indicated
Duration of study	Patients treated until disease progression, as defined by radiographic progression or unequivocal clinical progression (e.g. need for alternative anti-cancer therapy) The first patient was enrolled on 28.04.09 and the last patient was enrolled on 23.06.10. Follow-up is ongoing
Method of randomisation	Eligible patients were randomised (1:1) using a centralised IWRS/IVRS and were stratified by baseline ECOG PS grade (0 versus 1)
Method of blinding (care provider, patient and outcome assessor)	Double blind: patients and investigators were blinded to the study drug. Placebo matched the AA tablets in size, colour and shape. All patients, family members, study personnel, and members of the IDMC were to remain blinded to treatment assignment until completion of the study
Intervention(s) and comparator(s)	• AAP: AA (1 g q.d.) + prednisone/prednisolone (5 mg b.i.d.) until disease progression (N=546) • PP: placebo + prednisone/prednisolone (5 mg b.i.d.) until disease progression (N=542) Each treatment cycle was 28 days 

Primary outcomes (including scoring methods and timings of assessments)	The co-primary efficacy endpoints of this study were rPFS and OS. The outcome rPFS was the time from randomisation to the occurrence of one of the following, whichever occurred first: progression by bone scan (according to adapted PCWG2 criteria), progression by CT or MRI (according to modified RECIST criteria), or death (but not rising PSA). The rPFS distribution, median rPFS, and the 95% CIs were estimated using the Kaplan–Meier method. OS was measured from the date of randomisation to the date of all-cause death. OS data were collected throughout the study treatment phase and during follow-up. Survival time of living patients was censored at the last date a patient was known to be alive or lost to follow up. The OS distribution curve, median OS, and 95% CIs were estimated using the Kaplan–Meier method. Statistical inference was evaluated according to the group sequential testing design.
Secondary outcomes (including scoring methods and timings of assessments)	• Time from randomisation to first opiate use for cancer pain • Time from randomisation to initiation of cytotoxic chemotherapy for prostate cancer • Time from randomisation to first established clinical deterioration in terms of ECOG PS by ≥1 grade • Time from randomisation to first established PSA progression
Other endpoints	• PSA response rate • Objective response rate • Duration of response • Time from randomisation to first established analgesic progression • Functional status • Time from randomisation to first established functional status deterioration • Time from randomisation to first established progression in average pain intensity (BPI-SF) • Time from randomisation to first established progression in worst pain intensity (BPI-SF) • Time from randomisation to first established progression in pain interference
Planned analyses	• Single rPFS analysis at 100% of total expected rPFS events (378 events) • First interim OS analysis at 15% of total OS events (116 events) • Second interim OS analysis at 40% of total OS events (311 events) • Third interim OS analysis at 55% of total events (425 events) • Final OS analysis at 100% of total events (773 events)
Duration of follow-up	Patients were to be treated until disease progression. After discontinuing study treatment, patients were to be contacted every 3 months. Follow-up was to continue for up to 60 months or until the patient died, was lost to follow-up, or withdrew informed consent

SOURCE: COU-AA-302 study clinical study report (unpublished) [4;65] and Ryan et al. [59].
AA, abiraterone acetate; AAP, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory short form; CI, confidence interval; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; IDMC, Independent Data Monitoring Committee; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PCWG, Prostate Cancer Working Group; PP, placebo plus prednisone; PS, performance status; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria In Solid Tumors; rPFS, radiographic progression-free survival.

Participants

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

Patients in the COU-AA-302 study were defined as mCRPC patients who had relapsed following ADT and had not been previously treated with chemotherapy. These patients were asymptomatic or mildly symptomatic from prostate cancer, as defined by a BPI-SF score for question #3 (worst pain in last 24 hours on a scale of

0–10) of 0–1 (asymptomatic) or 2–3 (mildly symptomatic) and an ECOG PS score of 0 or 1. At baseline, patients had mean castrate testosterone concentrations of 0.3 ng/mL. Patients were not receiving opiates for cancer-related pain and had no measurable visceral or liver metastases. The full inclusion and exclusion criteria are given in Table 13.

Table 13: Eligibility criteria in the RCT COU-AA-302

Inclusion criteria	Exclusion criteria

• Male, ≥18 years of age
• Histologically or cytologically confirmed adenocarcinoma of the prostate
• Metastatic disease documented by positive bone scan or metastatic lesions, other than liver or visceral metastasis, on CT or MRI. If lymph node metastasis was the only evidence of metastasis, it must have been ≥2 cm in diameter
• Surgical or medical castration, as demonstrated by serum testosterone levels <50 ng/dL (<2.0 nM). If the patient was treated with LHRH agonists, the therapy must have been initiated ≥4 weeks prior to Cycle 1 Day 1 and must have continued throughout the study
• Documented prostate cancer progression by PSA, according to adapted PCWG2, or radiographic progression according to modified RECIST criteria
• Asymptomatic or mildly symptomatic from prostate cancer, as defined by a score of 0–1 (asymptomatic) or 2–3 (mildly symptomatic) for BPI-SF Question #3
• Previous antiandrogen therapy followed by documented PSA progression after discontinuing the antiandrogen (≥4 weeks since last flutamide, ≥6 weeks since last bicalutamide or nilutamide) prior to enrolment
• ECOG PS grade 0 or 1
• Haemoglobin ≥10.0 g/dL, independent of transfusion
• Platelet count ≥100,000/μL
• Serum albumin ≥3.5 g/dL
• Serum creatinine <1.5 x ULN or a calculated creatinine clearance ≥60 mL/min
• Serum potassium ≥3.5 mmol/L
• Adequate liver function as defined by:
  – Serum bilirubin <1.5 x ULN (except for patients with documented Gilbert's disease)
  – AST or ALT <2.5 x ULN
• Ability to swallow the study medication whole as a tablet
• Life expectancy ≥6 months
• Patients who had partners of childbearing potential must have been willing to use a
	• Use of opiate analgesics for cancer-related pain, including codeine and dextropropoxyphene, within 4 weeks of Cycle 1 Day 1
	• Prior cytotoxic chemotherapy or biological therapy for the treatment of CRPC
	• Radiation therapy for treatment of the primary tumour within 6 weeks of Cycle 1 Day 1
	• Radiation or radionuclide therapy for treatment of mCRPC
	• Prior therapy with ketoconazole for prostate cancer lasting >7 days
	• Prior systemic therapy with an azole drug (e.g. fluconazole, itraconazole) within 4 weeks of Cycle 1 Day 1
	• Prior flutamide treatment within 4 weeks of Cycle 1 Day 1 (patients whose PSA did not decline for ≥3 months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1)
	• Prior bicalutamide or nilutamide within 6 weeks of Cycle 1 Day 1 (patients whose PSA did not decline for ≥3 months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1)
	• Active infection or other medical condition that would have made prednisone (corticosteroid) use a contraindication
	• Any chronic medical condition that required a higher dose of corticosteroid than 5 mg b.i.d. prednisone
	• Pathological finding of small cell carcinoma of the prostate
	• Known liver, brain, or visceral organ metastasis
	• Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg). Patients with a history of hypertension were allowed, provided BP was controlled by antihypertensive therapy
	• Active or symptomatic viral hepatitis or chronic liver disease
	• History of pituitary or adrenal dysfunction
	• Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the 6 months prior to screening, severe or unstable angina, or NYHA Class II–IV heart disease or cardiac ejection fraction measurement of <50% at baseline
	• Atrial fibrillation, or other cardiac arrhythmia requiring medical therapy

method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after the last study medication administration • Able to provide written informed consent • Able to provide written Authorisation for Use and Release of Health and Research Study Information (US sites only) or Data Protection Consent (European sites only)	• Other malignancy, except non-melanoma skin cancer, with a ≥30% probability of recurrence within 24 months • 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 have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study

SOURCE: COU-AA-302 study clinical study report (unpublished) [4;65].
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BPI-SF, brief pain inventory short form; CRPC, castration-resistant prostate cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PCWG, Prostate Cancer Working Group; PS, performance status; PSA, prostate-specific antigen; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria In Solid Tumors; ULN, upper limit of normal.

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

Baseline patient demographics and disease characteristics were well balanced between the two treatment groups (Table 14). Approximately 3/4 of patients in both groups had a baseline ECOG PS score of 0, and 2/3 of patients were asymptomatic. All patients had received prior ADT.

Table 14: Characteristics of participants in the RCT by randomised group (ITT)

COU-AA-302 **Baseline characteristic**	**AAP** **(N=546)**	**PP** **(N=542)**
Age, years, mean (SD)	70.5 (8.8)	70.1 (8.7)
Male, %	100	100
White race N n (%)	 545 520 (95.4)	 540 510 (94.4)
Weight, kg N Mean (SD)	 527 88.5 (15.1)	 520 89.6 (17.0)
Height, cm N Mean (SD)	 539 174.7 (7.5)	 536 175.2 (7.9)
Time from initial diagnosis to first dose, years N Mean (SD)	 542 6.7 (4.9)	 540 6.5 (4.8)
PSA at initial diagnosis, ng/mL N Mean (SD)	 470 174.0 (540.4)	 454 219.7 (888.8)
Baseline PSA, ng/mL N Mean (SD)	 546 133.4 (323.6)	 539 127.6 (387.9)
TNM stage at initial diagnosis, n (%) Stage I Stage II Stage III	 1 (0.2) 86 (15.8) 52 (9.5)	 2 (0.4) 70 (12.9) 63 (11.6)

Stage IV	201 (36.8)	191 (35.2)
Incomplete reporting	206 (37.7)	216 (39.9)
Gleason score at initial diagnosis, n (%)		
N	488	508
<7	65 (13.3)	64 (12.6)
7	160 (32.8)	190 (37.4)
≥8	263 (53.9)	254 (50.0)
Extent of disease, n (%)		
N	544	542
Bone	452 (83.1)	432 (79.7)
Bone only	274 (50.4)	267 (49.3)
Soft tissue or node	267 (49.1)	271 (50.0)
Bone, soft tissue, or node	544 (100.0)	542 (100.0)
Other	4 (0.7)	7 (1.3)
Baseline BPI-SF #3 pain score (worst pain over last 24 hours), n (%)		
N	539	534
0–1	370 (68.6)	346 (64.8)
2–3	129 (23.9)	147 (27.5)
≥4	40 (7.4)	41 (7.7)
Mean (SD)	1.2 (1.7)	1.2 (1.6)
ECOG PS, n (%)		
0	413 (75.6)	409 (75.5)
1	133 (24.4)	133 (24.5)
Previous prostate cancer therapy, n (%)		
N	544	542
Surgery	256 (47.1)	244 (45.0)
Radiotherapy	283 (52.0)	303 (55.9)
Hormonal	544 (100.0)	542 (100.0)
Orchiectomy	20 (3.7)	24 (4.4)
Other	82 (15.1)	63 (11.6)

SOURCE: COU-AA-302 study clinical study report (unpublished) [65] and conference poster [74].
BPI-SF, brief pain inventory short form; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PS, performance status; PSA, prostate-specific antigen; RCT, randomised controlled trial; SD, standard deviation; TNM, tumour–node – metastasis.

Outcomes

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

The COU-AA-302 study examined two co-primary outcomes (OS and radiographic progression-free survival [rPFS]) and several secondary outcomes. These are described in Table 15. rPFS was chosen as a co-primary endpoint because: (1) collection of OS data can be a lengthy process; (2) the effect of subsequent active therapies may reduce the accuracy of the OS estimate; (3) PFS has been found to

predict OS in prostate cancer patients [82;83]; and (4) this approach was deemed appropriate by the CHMP and the US Food and Drug Administration (FDA) [84].

Table 15: Primary and secondary outcomes for COU-AA-302

	Outcome(s) and measures	**Definition of outcome**	**Reliability/validity/ current use in clinical practice**
Primary outcomes (co-primary outcomes)	rPFS	Time from randomisation to one of the following: progression by bone scan (adapted PCWG2 criteria) or CT or MRI (modified RECIST criteria) or death	Although PFS is not routinely used in clinical practice, it is a common endpoint used in oncology trials. A substantial improvement in rPFS is clinically meaningful to mCRPC patients as it delays the time to increased tumour burden, which may ultimately lead to the decision to initiate opiates or cytotoxic chemotherapy. Progression of metastatic bone disease is of paramount importance because of pain and skeletal morbidity
	OS	The time from randomisation to all-cause death	OS is a patient-relevant outcome and is the key outcome currently used to establish regulatory approval for new treatments
Secondary outcomes	Time to opiate use for cancer pain	The time from randomisation to opiate use for prostate cancer pain	This is an important outcome in clinical practice as it determines when patients have to receive opiates, which is a marker of severe pain and potentially of progression of metastatic bone disease
	Time to initiation of cytotoxic chemotherapy	The time from randomisation to initiation of cytotoxic chemotherapy for prostate cancer	This is an important outcome in clinical practice as it determines when patients have to receive docetaxel chemotherapy, which is used as an artificial boundary in the disease course of prostate cancer
	Time to deterioration in ECOG PS by ≥1 point	The time from randomisation to first ≥1 grade worsening in the ECOG PS scale	ECOG is routinely used to assess performance in prostate cancer patients in clinical practice, and is used to help determine whether patients are likely to tolerate chemotherapy
	Time to PSA progression	The time from randomisation to PSA progression, assessed by observation of trends in serial PSA measurements, according to adapted PCWG2 criteria	PSA progression is frequently used in England and Wales clinical practice to assess disease progression
Other outcomes	PSA response rate	The proportion of patients achieving a PSA decline ≥50% according to PCWG2 criteria	PSA response is a primary outcome measure by which the successful management of the disease is assessed

	Objective response rate in patients with measurable disease	The proportion of patients with measurable disease achieving a complete or partial response according to RECIST criteria (baseline lymph node size ≥2 cm to be considered a target lesion)	This is important in determining whether interventions are effecting a meaningful response
	Duration of response	The time from first response (in patients with measurable disease, according to modified RECIST criteria) to progression	This is a clinically relevant outcome as it may be used to determine when a patient needs to receive an additional or different intervention
	QoL total score and each subscale	HRQL as measured by the FACT-P instrument	QoL and other patient-reported outcomes are not routinely assessed in clinical practice in England and Wales, but are becoming increasingly important for treatment decisions
	Time to pain progression	The time from randomisation to first increase in pain (with the exact definition varying depending on the pain progression outcome measured, detailed in section 6.5)	This is a clinically relevant outcome that directly affects how a patient will be treated (i.e. dose and selection of analgesics), and may also reflect the occurrence of bone metastases
	Time to analgesic progression	Defined as a ≥30% increase in analgesic usage score from baseline that was observed at two consecutive evaluations ≥4 weeks apart. Analgesic scores were assessed according to the WHO scale (0 for no medication, 1 for non-opiate pain medication, 2 for opiates for moderate pain, 3 for opiates for severe pain)	This is a clinically relevant outcome that directly affects how a patient will be treated (i.e. the dose and selection of analgesics), and may also reflect the occurrence of bone metastases

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; OS, overall survival; PCWG, Prostate Cancer Working Group; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; rPFS, radiographic progression-free survival; WHO, World Health Organization.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

The primary hypothesis was that patients receiving AAP would have improved OS and/or rPFS compared with patients receiving PP. Therefore, OS and rPFS were co-

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

Time-to-event analyses (OS, PFS, time to progression) were compared between the two treatment groups using the log-rank test procedure in the ITT population according to the stratification factors specified at the time of randomisation.

Estimates of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were provided using a Cox proportional hazard model stratified by the same stratification factors specified at randomisation. Kaplan–Meier survival curves were generated. The chi square or Fischer's exact test methods were used to compare proportions.

The original protocol and statistical analysis plan for OS included two interim analyses (after 15% and 50% of 773 required OS events) and a final analysis (after 100% of the required OS events). However, this was amended, before the first interim OS analysis had been done, to three interim analyses (after 15%, 40%, and 55% of the required OS events). The additional interim analysis after 40% of OS events was added because a survival advantage was observed with AAP vs. PP in study COU-AA-301 (post-chemotherapy) [6;85]. Only one statistical analysis (by Independent Review) was planned for rPFS, when 378 rPFS events had occurred. This coincided with the first OS interim analysis and therefore, the first interim analysis included both OS and rPFS analyses. Updated analyses of rPFS to include additional events based on Investigator Review were also conducted at each of the subsequent OS interim analyses.

As the COU-AA-302 trial had co-primary endpoints of rPFS and OS, the p-value of 0.05 (i.e. the probability that an observed difference could have occurred by chance, 5% in this case) had to be shared amongst rPFS (which received 0.01, or 1%) and OS (which received 0.04, or 4%). In addition, the overall p-value of 0.04 for OS needed to be spread over multiple time points (after 15%, 40% and 55% of deaths). Therefore, the p-value at any of these time points had to be much lower than 0.04. Using the O'Brien-Fleming statistical stopping boundaries, as implemented by the Lan-DeMets alpha spending method, p values of <0.0001, 0.0005, and 0.0034 were required at the first, second, and third interim analyses, respectively, to show statistical significance for OS (Table 16).

This approach makes it more difficult to stop a study early for superiority and less difficult as the data get closer to full maturity or full information. The logic behind this approach is that at 40% information, for example, one has less than half the expected information, so the data ought to be more strongly convincing to suggest stopping the study.

The rule for creating the boundary values is called a spending function because one is 'spending' the type I error, spreading it out over multiple time points, i.e. the overall p value of 0.04 for OS is divided between the three interim analyses. O'Brien-Fleming stopping boundary makes it difficult to stop early unless there is very strong evidence for superiority. Simplistically, the significance level (p-value) that results in

a recommendation for early termination is a function of the amount of information obtained to date.

Table 16: COU-AA-302 study planned rPFS and OS analyses

Variable	rPFS analysis	OS analyses			
	Single planned analysis	Interim 1[a]	Interim 2	Interim 3	Final
Percentage of total events	~100	~15	40	55	100
Projected observed events	378	116	311	425	773[b]
Efficacy boundary (HR)	0.667	0.336	0.672	0.751	0.861
Projected cumulative stop probability under (H_0)	–	<0.0001	0.0005	0.0034	0.04
Actual data cut-off date for the analysis	20.12.10	20.12.10	20.12.11	22.05.12	Projected to be 31.03.14

SOURCE: COU-AA-302 study clinical study report (unpublished) [18;65].
[a]At the time of rPFS analysis.
[b]Required to detect a difference between a median OS of 22 months in the placebo group and a median OS of 27.5 months in the abiraterone acetate group (HR=0.80) at the 2-tailed significance level of 0.04 with a power of 85%.
HR, hazard ratio; OS, overall survival; rPFS, radiographic progression-free survival.

The planned sample size of approximately 1,000 patients (randomised 1:1 to AAP or PP) provided 85% power to detect a difference between a median OS of 27.5 months in the AAP group and a median OS of 22 months in the PP group (HR=0.80) under the assumption of a two-tailed significance level of 0.04 and required 773 deaths to have occurred. This planned sample size also provided 91% power to detect a difference between median rPFS of 6 months for the AAP group and a median rPFS of 4 months in the PP group (HR=0.667) under the assumption of an exponential model with proportional hazards and a two-tailed level of significance of 0.01 and required 378 rPFS events to have occurred.

Reasons for patient discontinuation included: unequivocal clinical progression; sustained side effects; initiation of new anticancer treatment; administration of prohibited medications; and patient withdrawal of consent.

Survival time of living patients was censored at the last date they were known to be alive or lost to follow-up as of the cut-off date for the interim analysis database lock. In the analysis of rPFS, the following censoring rules applied:

- If the patient did not have a baseline scan or on-study scans, the patient was to be censored on the date of randomisation
- If the patient did not show progression according to modified RECIST or bone scan, the patient was to be censored on the date of the last scheduled scan
- Patients were to be censored on the date of the last scan that showed no disease progression if the patient received another therapy (i.e. cytotoxic chemotherapy) known or intended for the treatment of mCRPC during the study; or the subject missed ≥2 planned radiographic scans or had ≥2 consecutive unreadable scans.

Patients with no opiate use at the time of analysis were censored at the last known date of no opiate use; subjects with no opiate use assessment were censored at the date of randomisation. Similarly for: no cytotoxic chemotherapy, no ECOG PS

deterioration, no PSA progression, no pain progression, no worst pain intensity progression, and no progression in analgesic use.

6.3.7 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 whether the observed treatment effects were seen consistently in subgroups for the co-primary rPFS and OS outcomes. The following subgroups were pre-specified *a priori* in the statistical analysis plan:

- Patients whose baseline PSA, lactate dehydrogenase (LDH), and alkaline phosphatase concentrations were over versus under the median baseline concentrations
- Patients within and outside North America.
- ECOG PS score: 0 versus 1
- Pain: BPI-SF question #3 0–1 versus 2–3
- Bone metastases only at entry (present versus absent).
- Baseline age (<65, ≥65, and ≥75 years).

Treatment exposure time (<3, 12–15, and ≥24 months) was also explored, but was not pre-specified.

Results from the subgroup analyses were to be considered consistent with the primary (ITT) analysis if the 95% CIs for the HRs within a subgroup included the point estimate for the primary analysis.

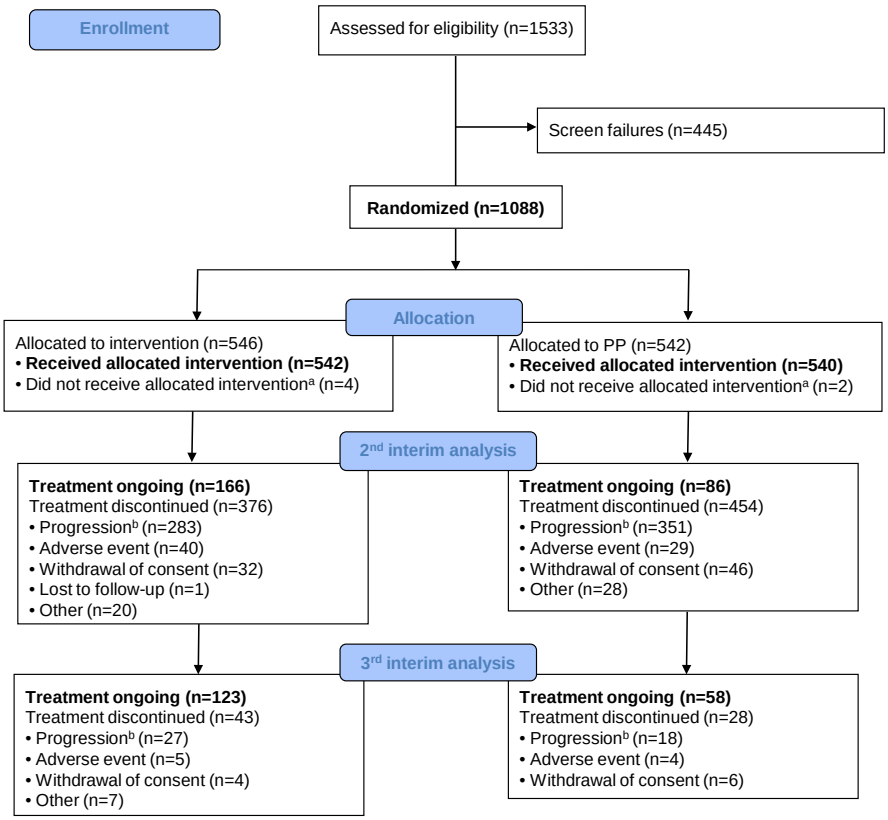
The NICE scope document questioned whether AA is likely to be more effective in asymptomatic or mildly symptomatic men. Hence, we estimated cost-effectiveness among asymptomatic men (i.e. BPI-SF score for question #3 [worst pain in last 24 hours on a scale of 0–10] of 0–1). We also estimated cost-effectiveness in the subgroup of patients with ECOG 0.

Participant flow

6.3.8 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.

The ITT population consisted of 1,088 patients; and the safety population consisted of 1,082 patients (Figure 3).

Figure 3: COU-AA-302 study patient flow diagram (data from third interim analysis)

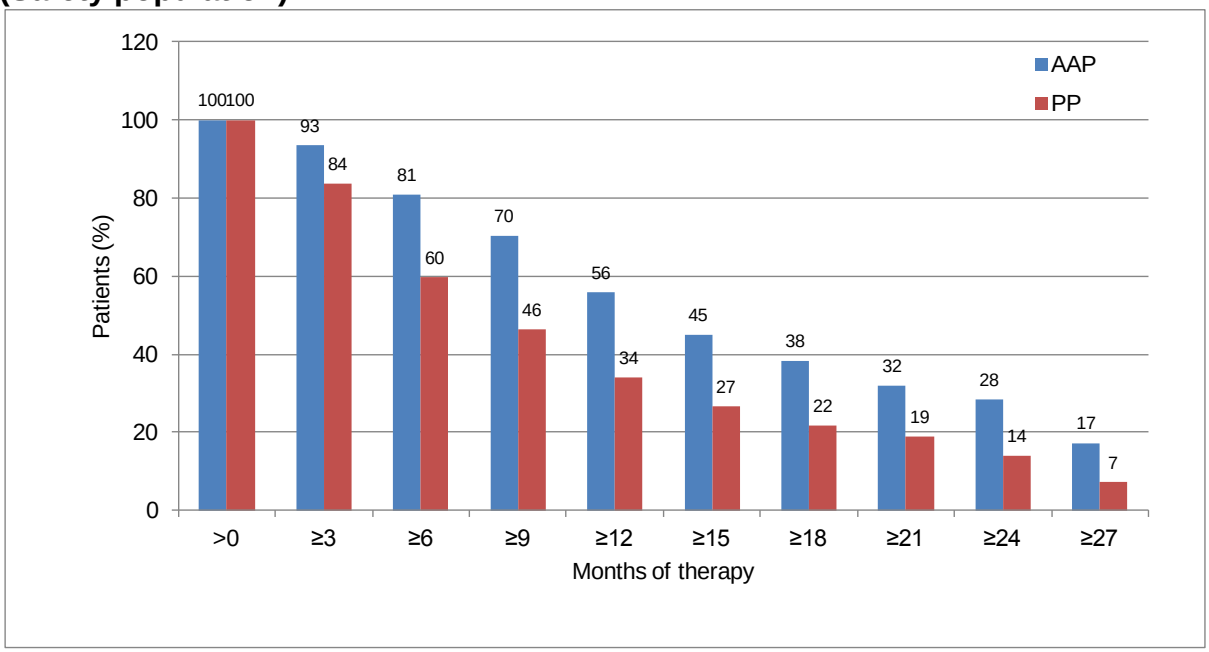


SOURCE: COU-AA-302 study clinical study reports (unpublished) [18;65].
[a]Five patients were mistakenly randomised instead of indicating them as screening failures; one patient (AAP arm) withdrew consent after randomisation but before starting treatment.
[b]Radiographic and/or unequivocal clinical progression.
AAP, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; PP, placebo plus prednisone.

Treatment exposure

Patients continued treatment with AAP or PP until disease progression (determined according to radiographic and clinical measures). The median treatment duration was 13.8 months (15 cycles initiated) in the AAP arm and 8.3 months (nine cycles initiated) in the PP arm. Information regarding the cumulative treatment duration is summarised in Figure 4.

Figure 4: Extent of exposure, cumulative summary at 3rd interim analysis (Safety population)



SOURCE: COU-AA-302 study clinical study report (unpublished) [18].

Treatment discontinuation

The most common reason for discontinuation by the third interim analysis was disease progression, which was observed in 57% and 68% of patients in the AAP and PP groups, respectively (Table 17). AEs that led to discontinuation of AAP or PP (not including discontinuations of prednisone/prednisolone only) were observed in 8% and 6%, respectively.

Table 17: Treatment discontinuations at the third interim OS analysis (22.05.12; Safety population)

	AAP (N=542)	**PP (N=540)**
Patients treated, n (%)	542 (100.0)	540 (100.0)
Treatment discontinued	419 (77.3)	482 (89.3)
Treatment ongoing	123 (22.7)	58 (10.7)
Reasons for discontinuation, n (%)		
Radiographic and unequivocal clinical progression	66 (12.2)	56 (10.4)
Radiographic progression only	126 (23.2)	172 (31.9)
Unequivocal clinical progression only	118 (21.8)	141 (26.1)
AE	45 (8.3)	33 (6.1)
Withdrawal of consent to treatment	36 (6.6)	52 (9.6)
Other	27 (5.0)	28 (5.2)
Lost to follow-up	1 (0.2)	0

SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AAP, abiraterone acetate plus prednisone/prednisolone; AE, adverse event; OS, overall survival; PP, placebo plus prednisone/prednisolone.

Cross-over

Cross-over from PP to AAP occurred following unblinding (02.04.12) for three patients by the third interim analysis (22.05.12). Any effect on the third interim analysis results is expected to be minimal due to the few patients involved and the short time between unblinding and the third interim analysis.

6.4 Critical appraisal of relevant RCTs

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

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

Table 18: Quality assessment results for the COU-AA-302 study

Trial no. (acronym)	**COU-AA-302**
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes[a]
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[a]
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes

[a]During 15/12/11–29/3/12, 62 patients received marked AA tables (rather than plain tablets), and it is possible that two patients may have realised that they were in the AAP group 5 days before the second data cut-off. This is unlikely to have had any impact on the results. For further details, please see section 10.3.

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

A detailed quality assessment of the COU-AA-302 study is provided in appendix 3.

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

There is only one RCT.

6.5 Results of the relevant RCTs

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

Results presented in the following section are based on the results from the second (data cut-off 20/12/11; published [59]) and third (data cut-off 22/5/12; unpublished CSR [18] and published abstracts [60;69-74]) interim analyses of the COU-AA-302 study, which were conducted after approximately 40% and 55% of the total OS events had occurred. Efficacy analyses were performed using the ITT population, which included all randomised patients.

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

Kaplan–Meier plots for the co-primary outcomes are shown in section 6.5.3. Those for secondary outcomes are shown in appendix 14.

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

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.**
- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**

- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

Co-primary efficacy outcome – rPFS

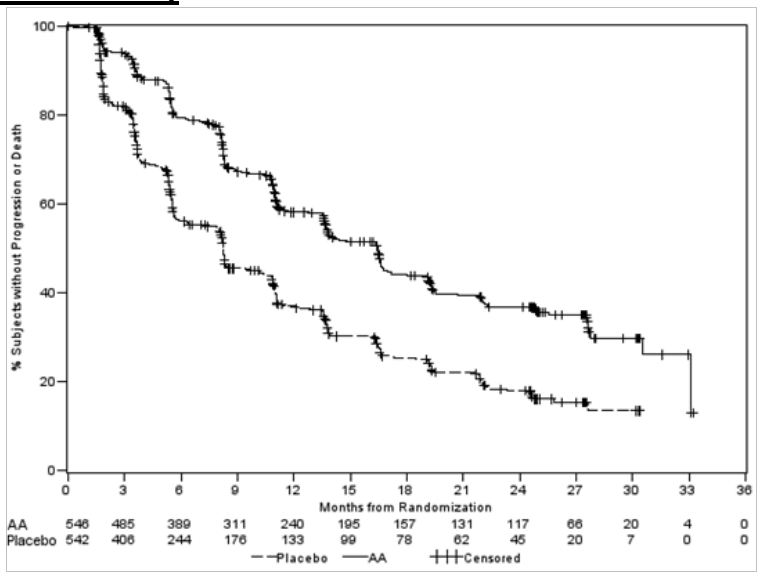
Treatment with AAP resulted in a 48% relative reduction in the risk of radiographic progression compared with PP (absolute risk reduction 11.5%), and increased PFS by 8.2 months (Table 19). The Kaplan–Meier plot for rPFS (3rd interim analysis) is presented in Figure 5.

Table 19: rPFS in patients treated with either AAP or PP (ITT)

	Interim analysis 2		**Interim analysis 3**	
	AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
Number of patients with PFS event, n (%)	271 (49.6)	336 (62.0)	292 (53.5)	352 (64.9)
Time-to-event[a] (months), median (95% CI)	16.5 (13.8, 16.8)	8.3 (8.1, 9.4)	16.5 (13.8, 16.8)	8.2 (8.0, 9.4)
HR (95% CI)[a]	0.53 (0.45, 0.62)		0.52 (0.45, 0.62)	
p value[b]	<0.0001		<0.0001	

SOURCES: Ryan et al. (published; interim analysis 2) [59], COU-AA-302 clinical study report (unpublished; interim analysis 2) [65] and COU-AA-302 study clinical study report [18] (unpublished; interim analysis 3).
[a]HR is from a stratified proportional hazards Cox model. HRs <1 favour AAP.
[b]p value is from a log-rank test stratified by ECOG PS score (0 or 1).
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival; PP, placebo plus prednisone/prednisolone.

Figure 5: Kaplan–Meier curve of rPFS – ITT population (third interim analysis – 22.05.12, 55% data cut-off)



SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AA, abiraterone acetate plus prednisone; ITT, intent-to-treat; Placebo, placebo plus prednisone; rPFS, radiographic progression-free survival.

Co-primary efficacy outcome – OS

At the IA3 cut-off date (22.05.12), 434 death events had been observed (200 [36.6%] in the AAP group and 234 [43.2%] in the PP group). Treatment with AAP was

associated with a clinically meaningful increase in OS compared with PP treatment, representing a 21% decrease in the relative risk of death (absolute risk reduction 6.5%), and an increase in OS of 5.2 months (Table 20). This exceeds the 3-month extension to life criterion set out in the NICE policy on appraising life-extending, end-of-life medicines [39]. The Kaplan–Meier plot for OS (3rd interim analysis) is presented in Figure 6.

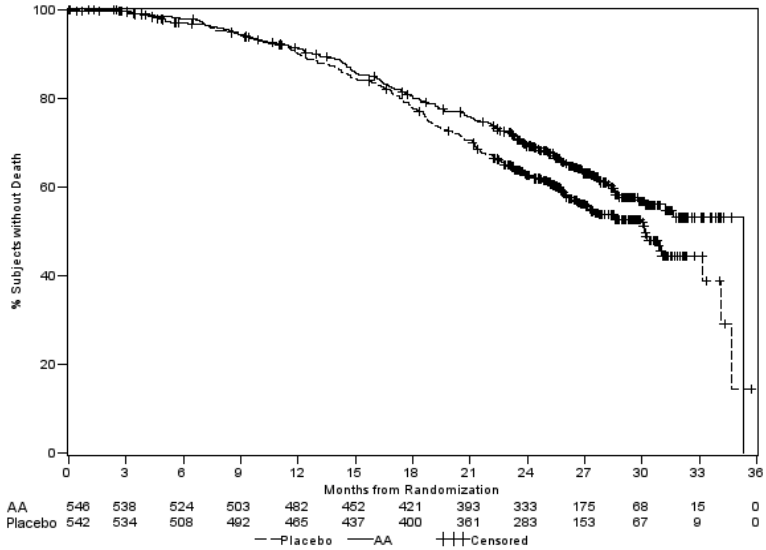
The point estimates for the HR (0.75 and 0.79 at the second and third interim analyses, respectively; Table 20) were lower than the hypothesised treatment effect size of 0.80, representing a clinically meaningful result. However, neither the second nor third interim analysis OS results met the stringent pre-specified statistical significance levels (please see section 6.3.6 for further information). Despite this, the study was halted by the IDMC between these two analyses because the very significant rPFS results, impressive results for the secondary endpoints, and a clear trend toward improvement in OS demonstrated a 'highly significant advantage' for patients in 'Arm X' (AAP). The IDMC therefore halted the study to allow cross-over from PP to AAP, as not doing so would have been unethical. Only three patients had crossed over from PP to AAP by the third interim analysis.

Table 20: OS of patients treated with either AAP or PP (ITT)

	Interim analysis 2		**Interim analysis 3**	
	AAP (N=546)	**PP (N=542)**	**AAP (N=546)**	**PP (N=542)**
Number of deaths, n (%)	147 (26.9)	186 (34.3)	200 (36.6)	234 (43.2)
OS[a] (months), median (95% CI)	NR (NR, NR)	27.2 (26.0, NR)	35.3 (31.2, 35.3)	30.1 (27.3, 34.1)
HR (95% CI)[b]	0.75 (0.61, 0.93)		0.79 (0.66, 0.96)	
p value[c]	0.0097		0.0151	
p value required for significance	0.0005		0.0034	

SOURCES: Ryan et al. (published; interim analysis 2) [59], review article [64] and COU-AA-302 study clinical study report [18] (unpublished; interim analysis 3).
[a]Survival time of living patients was censored at the last date a patients was known to be alive or lost to follow-up as of the cut-off date for the interim analysis.
[b]HRs from a stratified proportional hazards Cox model. HRs <1 favour AAP.
[c]p value from a log-rank test stratified by ECOG PS score (0 or 1).
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NR, not reached; OS, overall survival; PP, placebo plus prednisone/prednisolone.

Figure 6: Kaplan–Meier curve of OS – ITT population (COU-AA-302 study third interim analysis)



SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AA, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; OS, overall survival; Placebo, placebo plus prednisone/prednisolone.

Impact of subsequent therapy on primary outcomes

Subjects in study COU-AA-302 were permitted to start new therapies following disease progression. At IA3, 622 patients (57%) had gone on to receive subsequent therapies, most commonly docetaxel (43.8% of AAP and 56.1% of PP patients) (Table 21). Seven percent of AAP and 14.4% of PP patients received AAP as subsequent therapy (Table 21). The impact of moving to subsequent therapies was explored in three pre-specified sensitivity analyses. Each analysis was compared at a two-sided significance level of 0.05. The effect size, once subsequent AAP treatment had been accounted for, was similar to the ITT effect size (HR was 0.01 less than the non-adjusted analysis) (Table 22).

Table 21: Selected subsequent therapy for prostate cancer – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

Subsequent therapy, n (%)	AAP (N=546)	PP (N=542)
Number of subjects with selected subsequent therapy for prostate cancer	274 (50.2)	348 (64.2)
Docetaxel	239 (43.8)	304 (56.1)
Cabazitaxel	60 (11.0)	70 (12.9)
Ketoconazole	39 (7.1)	63 (11.6)
AAP	38 (7.0)	78 (14.4)
Sipuleucel-T	33 (6.0)	28 (5.2)

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AAP, abiraterone acetate plus prednisone; ITT, intent-to-treat; PP, placebo plus prednisone.

Table 22: OS analyses of PP patients receiving subsequent therapy with AA at IA3, 22.05.12, 55% data cut-off (ITT population)

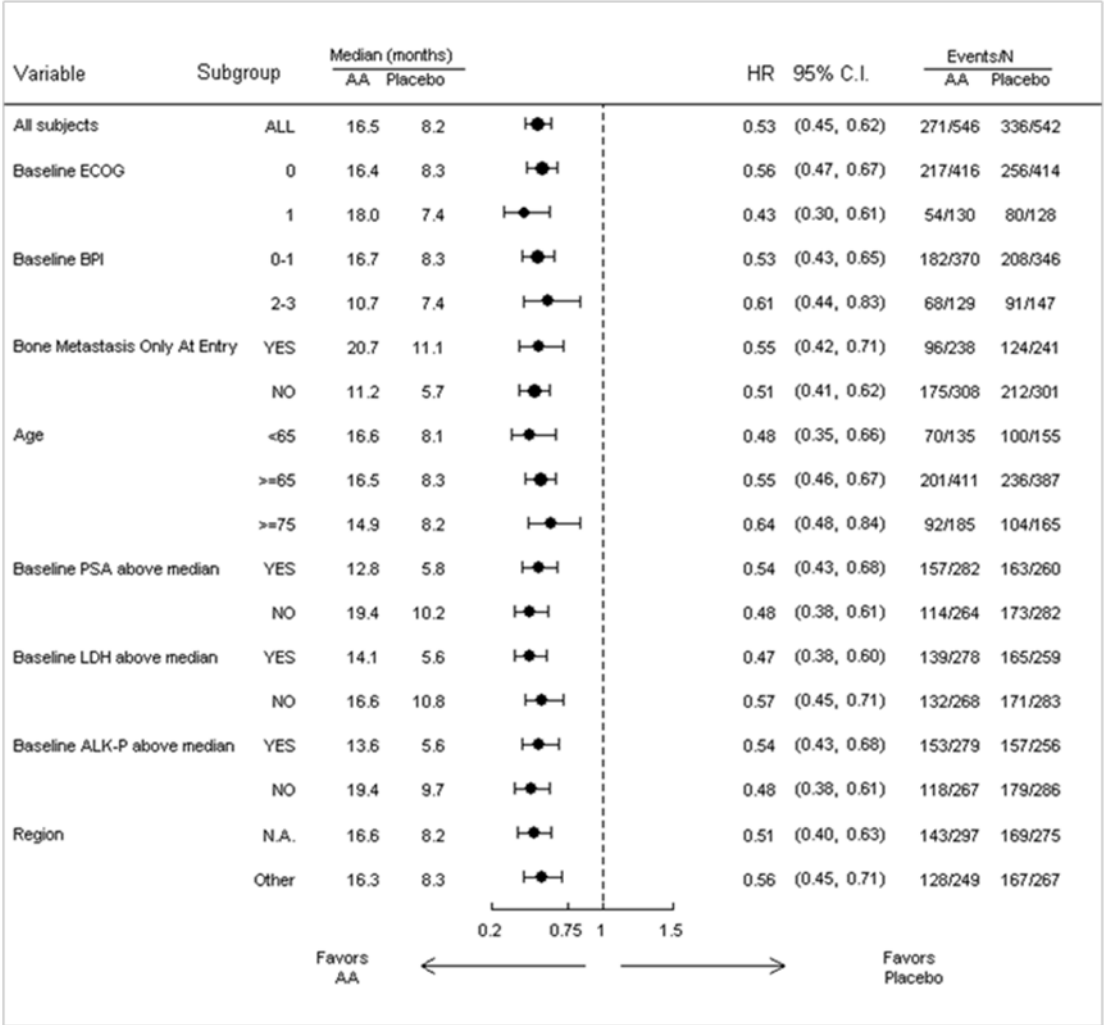
Analysis method	HR (95% CI)
Iterative Parameter Estimate	0.78 (0.63, 0.93)
Rank preserving failure time model	0.78 (0.64, 0.95)

CI, confidence interval; HR, hazard ratio.
Source: Report of updated data from study COU-AA-302 22 May 2012 data cut-off (unpublished) [18].

Co-primary efficacy outcomes – rPFS subgroup analyses

The prognostic factors considered in the pre-planned subgroup analyses for rPFS are listed in section 6.3.7. The rPFS results were consistently in favour of AAP across all subgroups examined (Figure 7). All estimated HRs and 95% CIs were below the threshold of no treatment effect (HR=1.0). This demonstrates that AAP significantly delayed disease progression compared to PP, irrespective of various patient characteristics.

Figure 7: rPFS subgroup analyses results, IA3, 22 May 2012, 55% data cut-off (ITT population): study COU-AA-302



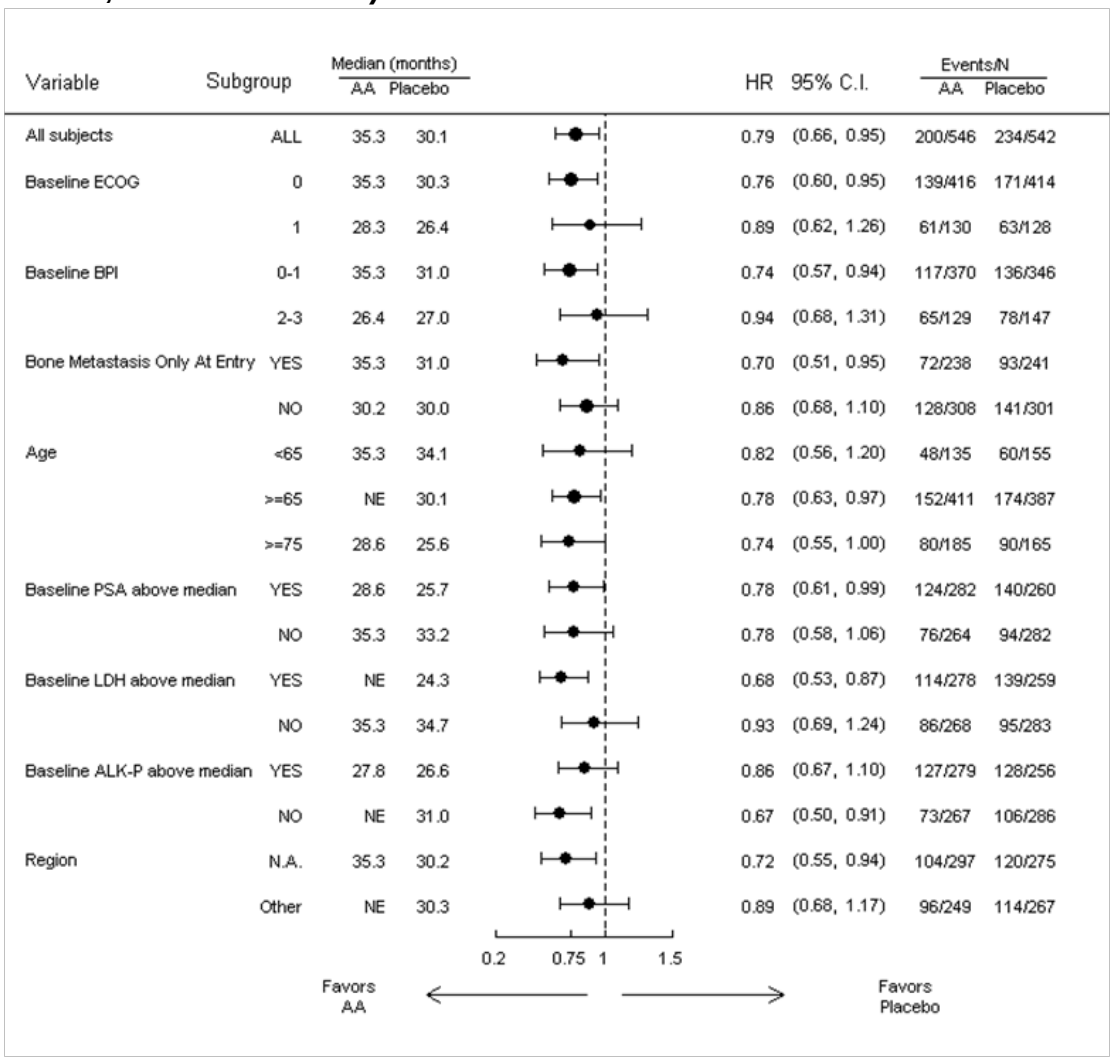
Variable	Subgroup	Median (months) AA	Median (months) Placebo	HR	95% C.I.	Events/N AA	Events/N Placebo
All subjects	ALL	16.5	8.2	0.53	(0.45, 0.62)	271/546	336/542
Baseline ECOG	0	16.4	8.3	0.56	(0.47, 0.67)	217/416	256/414
	1	18.0	7.4	0.43	(0.30, 0.61)	54/130	80/128
Baseline BPI	0-1	16.7	8.3	0.53	(0.43, 0.65)	182/370	208/346
	2-3	10.7	7.4	0.61	(0.44, 0.83)	68/129	91/147
Bone Metastasis Only At Entry	YES	20.7	11.1	0.55	(0.42, 0.71)	96/238	124/241
	NO	11.2	5.7	0.51	(0.41, 0.62)	175/308	212/301
Age	<65	16.6	8.1	0.48	(0.35, 0.66)	70/135	100/155
	>=65	16.5	8.3	0.55	(0.46, 0.67)	201/411	236/387
	>=75	14.9	8.2	0.64	(0.48, 0.84)	92/185	104/165
Baseline PSA above median	YES	12.8	5.8	0.54	(0.43, 0.68)	157/282	163/260
	NO	19.4	10.2	0.48	(0.38, 0.61)	114/264	173/282
Baseline LDH above median	YES	14.1	5.6	0.47	(0.38, 0.60)	139/278	165/259
	NO	16.6	10.8	0.57	(0.45, 0.71)	132/268	171/283
Baseline ALK-P above median	YES	13.6	5.6	0.54	(0.43, 0.68)	153/279	157/256
	NO	19.4	9.7	0.48	(0.38, 0.61)	118/267	179/286
Region	N.A.	16.6	8.2	0.51	(0.40, 0.63)	143/297	169/275
	Other	16.3	8.3	0.56	(0.45, 0.71)	128/249	167/267

SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AA, abiraterone acetate plus prednisone; ALK-P, alkaline phosphatase; BPI, brief pain inventory; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; LDH, lactate dehydrogenase; N.A., North America; Placebo, placebo plus prednisone; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

Co-primary efficacy outcome – OS subgroup analysis

The prognostic factors considered in the pre-planned subgroup analyses for OS are listed in section 6.3.7. The results for each subgroup analysis are shown as a forest plot (Figure 8). OS benefit was consistent across the subgroups studied. While 95% CIs crossed the threshold of no treatment effect (HR=1.0) in some cases, all point estimates were below this threshold, favouring AAP over PP.

Figure 8: OS subgroup analyses results – ITT population (third interim analysis – 22.05.12, 55% data cut-off)



SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AA, abiraterone acetate plus prednisone; ALK-P, alkaline phosphatase; BPI, brief pain inventory; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; LDH, lactate dehydrogenase; N.A., North America; NE, not estimable; OS, overall survival; Placebo, placebo plus prednisone; PSA, prostate-specific antigen.

Post-hoc analyses

Co-primary efficacy outcomes – Association of rPFS and OS

A supplementary analysis was performed to assess the strength of association between rPFS and OS using COU-AA-302 data. The strength of association was evaluated by Spearman's correlation via the Clayton copula, which takes censoring into account [86;87]. A positive association between rPFS and OS was observed, with an estimated coefficient of 0.72 [65;87], indicating that the rPFS data support the substantial prolongation of OS with AAP in this patient population.

OS after controlling for baseline imbalances

A post-hoc multivariate analysis for OS was also conducted to evaluate the treatment effect after controlling for any baseline prognostic factor imbalances (ECOG PS, PSA, LDH, alkaline phosphatase, haemoglobin, bone metastasis only,

age). AAP treatment resulted in a 26% decrease in the risk of death compared with PP (HR=0.74; 95% CI 0.61–0.89; p=0.0017).

Secondary efficacy outcomes – Time to disease state progression outcomes
The median follow-up duration for both treatment groups combined was 27.1 months. Significant differences in favour of the AAP group compared to the PP group were observed for all secondary efficacy outcomes (see Table 15), as shown in Table 23. Kaplan–Meier plots for these outcomes are presented in appendix 14 (section 10.14.1).

Table 23: Time to disease state progression outcomes results – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

Endpoint	Median, months (95% CI)		Difference, months	HR (95% CI)[a]	p value[b]
	AAP	PP			
Time to opiate use for cancer pain	NE (28.3, NE)	23.7 (20.4, 30.3)	NE	0.71 (0.59, 0.85)	0.0002
Time to initiation of cytotoxic chemotherapy	26.5 (23.5, 29.1)	16.8 (14.5, 19.4)	9.7	0.61 (0.51, 0.72)	<0.0001
Time to PSA progression	11.1 (8.5, 11.2)	5.6 (5.4, 5.6)	5.5	0.50 (0.43, 0.58)	<0.0001
Time to deterioration in ECOG PS (≥1 increase)	12.3 (11.3, 14.3)	10.9 (9.5, 11.8)	1.4	0.83 (0.72, 0.94)	0.0052

SOURCE: review article [64] and COU-AA-302 study clinical study report (unpublished) [18].
[a]HR is from stratified proportional hazards model. HR<1 favours AAP.
[b]p value is from a log-rank test stratified by ECOG PS grade (0 or 1).
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; PP, placebo plus prednisone/prednisolone; PS, performance status; PSA, prostate-specific antigen.

Other efficacy outcomes
Significant differences in favour of the AAP group were observed for: PSA response, objective response rate (complete or partial response according to modified RECIST criteria), and duration of response (appendix 14 [section 10.14.2]). There was also a significantly higher PSA response rate (≥50% decline from baseline according to adapted PCWG2 criteria) in the AAP group ([redacted]) [18]. Best overall response results were also in favour of AAP (appendix 14 [sections 10.14.2 and 10.14.3]).

All of the pain-related other efficacy outcomes were in favour of AAP, with significant differences for some of the outcomes (appendix 14 [section 10.14.2]). Kaplan–Meier plots for all pain-related outcomes are presented in appendix 14 (section 10.14.3).

HRQL was assessed in the COU-AA-302 study via the FACT-P instrument, and results of the second interim analysis have recently been published [66]. A summary of the time to a decrease of ≥10 points for all FACT-P subscale results at the time of the third interim OS analysis is presented in Table 24. Kaplan–Meier plots of the HRQL data are presented in appendix 14 (section 10.14.3).

Table 24: HRQL outcomes results – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

FACT-P Subscale	Median (95% CI) time to progression[a] (months)		HR of AAP/PP (95% CI)	p value
	AAP	PP		
FACT-P (Total Score)	12.7 (11.1, 14.0)	8.3 (7.4, 10.6)	0.79 (0.67, 0.93)	0.0046
PCS	11.1 (8.6, 13.8)	5.8 (5.5, 8.3)	0.72 (0.61, 0.84)	<0.0001
TOI	13.9 (12.0, 16.5)	9.3 (8.3, 11.1)	0.77 (0.65, 0.91)	0.0018
FACT-G	16.6 (13.8, 19.4)	11.1 (8.5, 14.0)	0.76 (0.64, 0.91)	0.0023
PWB	14.8 (13.6, 16.8)	11.1 (9.1, 13.8)	0.76 (0.64, 0.91)	0.0019
SFWB	18.4 (13.8, 24.8)	16.6 (11.1, NE)	0.95 (0.78, 1.15)	0.5774
EWB	22.5 (17.4, 27.9)	14.2 (13.3, 19.5)	0.73 (0.61, 0.89)	0.0017
FWB	13.3 (11.0, 15.7)	8.4 (6.5, 10.1)	0.77 (0.65, 0.91)	0.0016

SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference abstract [73].
[a]Decrease of ≥10 points.
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; EWB, emotional well being; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P: Functional Assessment of Cancer Therapy – Prostate; FWB, functional well being; HR, hazard ratio; ITT, intent-to-treat; PCS, Prostate Cancer Scale; PP, placebo plus prednisone; PWB, physical well being; SFWB, social/family well being; TOI, Total Outcome Index.

Summary – clinical data

- Treatment with AAP resulted in a significant and persistent delay in rPFS
  - AAP provided a 48% reduction in the risk of progression (HR=0.52; 95% CI 0.45, 0.62; p<0.0001) compared with PP, and increased rPFS by 8.2 months
  - This treatment effect was favourable and significant across all pre-specified subgroups (all HRs and 95% CIs <1).
- Treatment with AAP resulted in a clinically meaningful improvement in OS
  - AAP provided a 21% reduction in the risk of death (HR=0.79; 95% CI 0.66, 0.96; p=0.0151) compared with PP, and increased survival by 5.2 months
  - Improvement in OS was consistent and compelling across all pre-specified subgroups (all HRs <1.0).
- rPFS was highly correlated with OS (r=0.72), supporting the impact of AAP on OS.
- The durable clinical benefits of AAP observed after the second interim analysis resulted in the IDMC's unanimous recommendation to unblind the trial and allow crossover of PP patients to AAP. This decision underscored the strength of the evidence for AAP.

6.6 Meta-analysis

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

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**

- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

A meta-analysis is not appropriate as only a single RCT that compared AAP to PP in the treatment of asymptomatic or mildly asymptomatic patients with mCRPC was identified by the systematic review (as described in sections 6.1 and 6.2).

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

N/A.

6.6.3 If any of the relevant RCTs listed in response to section 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.

N/A.

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

N/A, as no indirect or mixed treatment comparisons were performed.

6.7.2 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.

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

6.7.6 Please present the results of the analysis.

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

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

N/A, as no indirect or mixed treatment comparisons were performed.

6.8 Non-RCT evidence

6.8.1 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, detailed in section 6.1 and 6.2, was conducted to identify all RCT and non-RCT evidence relevant to the current decision problem.

The systematic review identified two non-RCT studies involving AAP in a post-ADT, pre-chemotherapy mCRPC patient population as summarised in section 6.2.7. As both of these studies were open-label, single-arm, dose ranging studies [62;63], which did not administer AAP in the fashion specified in the market authorisation, neither were considered to contribute to the evidence base relevant to the decision problem of this submission.

6.9 Adverse events

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

The systematic review (described in sections 6.1 and 6.2) identified one RCT, COU-AA-302, that collected data on AEs associated with the administration of AAP [18;72;74]. The two non-RCTs (COU-AA-001 and COU-AA-002) [62;63] identified by the same overarching systematic review intended to determine the maximum tolerated dose of AAP in post-ADT, pre-chemotherapy patients with mCRPC but did not administer AA as per the marketing authorisation. Therefore, AEs from the two non-RCTs are not reported in this submission. No trials were identified in the systematic review that were specifically powered to assess the safety of AAP.

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

In the COU-AA-302 study, the median duration of treatment exposure was longer in the AAP group than in the PP group (13.8 vs. 8.3 months). Overall safety and tolerability data are shown Table 25.

Table 25: Overall safety results – safety population (third interim analysis – 22.05.12, 55% data cut-off)

Safety outcome, n (%)	AAP (N=542)	PP (N=540)	RR (95% CI)[a]
Number of patients with TEAEs[b]	538 (99.3)	524 (97.0)	1.02 (1.01, 1.04)
Drug-related[c]	426 (78.6)	414 (76.7)	1.03 (0.96, 1.09)
Number of patients with grade 3–4 TEAEs	267 (49.3)	235 (43.5)	1.13 (1.00, 1.29)
Drug-related[c]	127 (23.4)	97 (18.0)	1.30 (1.03, 1.65)
Number of patients with treatment-emergent SAEs[b]	188 (34.7)	146 (27.0)	1.28 (1.07, 1.54)

Drug-related[c]	63 (11.6)	55 (10.2)	1.14 (0.81, 1.61)
Grade 3–4	156 (28.8)	123 (22.8)	1.26 (1.03, 1.55)
Number of patients with TEAEs leading to treatment discontinuation[d]	58 (10.7)	53 (9.8)	1.09 (0.77, 1.55)
Drug-related[c]	32 (5.9)	24 (4.4)	1.33 (0.79, 2.22)
Number of patients with TEAE leading to death	21 (3.9)	16 (3.0)	1.31 (0.69, 2.48)
Drug-related[c]	6 (1.1)	6 (1.1)	1.00 (0.32, 3.07)
All deaths within 30 days of last dose	18 (3.3)	11 (2.0)	1.63 (0.78, 3.42)
Other	11 (2.0)	6 (1.1)	1.83 (0.68, 4.90)
Death due to prostate cancer	6 (1.1)	4 (0.7)	1.49 (0.42, 5.27)
Unknown	1 (0.2)	1 (0.2)	1.00 (0.06, 15.89)

[a]Calculated using http://www.hutchon.net/confidrr.htm. Values in bold indicate statistically significant results.
[b]Does not include grade 5 events.
[c]AEs reported as unlikely, possibly, or related to AA, prednisone/prednisolone, or placebo are classified as drug-related AEs.
[d]Discontinuation of study medication includes discontinuation of AA, prednisone/prednisolone, or placebo.
AAP, abiraterone acetate plus prednisone/prednisolone; PP, placebo plus prednisone/prednisolone; RR, relative risk; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The incidences of individual AEs that occurred in ≥5% of patients in either group are summarised in Table 26. The most frequently reported AEs were fatigue (39.7% AAP vs. 34.6% PP), back pain (33.2% vs. 33.1%), arthralgia (29.3% vs. 24.4%), nausea (24.0% vs. 23.0%), peripheral oedema (26.0% vs. 20.9%), constipation (23.6% vs. 20.4%), diarrhoea (23.4% vs. 18.1%) and hot flush (22.7% vs. 18.3%). The majority of these events were grade 1–2.

Table 26: Incidence of all AEs occurring in ≥5% of patients in either group (COU-AA-302 study third interim analysis, 55% data cut-off)

System organ/class/AEs, n (%)	AAP (N=542)	PP (N=540)	RR (95% CI)[a]
Total	538 (99.3)	524 (97.0)	1.02 (1.01, 1.04)
Musculoskeletal and connective tissue disorders	406 (74.9)	409 (75.7)	0.99 (0.92, 1.06)
Back pain	180 (33.2)	179 (33.1)	1.00 (0.85, 1.19)
Arthralgia	159 (29.3)	132 (24.4)	1.20 (0.98, 1.46)
Bone pain	113 (20.8)	103 (19.1)	1.09 (0.86, 1.39)
Pain in extremity	93 (17.2)	87 (16.1)	1.07 (0.82, 1.39)
Musculoskeletal pain	88 (16.2)	81 (15.0)	1.08 (0.82, 1.43)
Muscle spasms	77 (14.2)	111 (20.6)	0.69 (0.53, 0.90)
Groin pain	38 (7.0)	22 (4.1)	1.72 (1.03, 2.87)
Myalgia	35 (6.5)	32 (5.9)	1.09 (0.68, 1.73)
Muscular weakness	32 (5.9)	42 (7.8)	0.76 (0.49, 1.18)
Flank pain	27 (5.0)	17 (3.1)	1.58 (0.87, 2.87)
General disorders and administration site conditions	361 (66.6)	314 (58.1)	1.15 (1.04, 1.26)
Fatigue	215 (39.7)	187 (34.6)	1.15 (0.98, 1.34)
Oedema peripheral	141 (26.0)	113 (20.9)	1.24 (1.00, 1.54)
Pyrexia	52 (9.6)	34 (6.3)	1.52 (1.01, 2.31)
Asthenia	47 (8.7)	47 (8.7)	1.00 (0.68, 1.47)
Gastrointestinal disorders	356 (65.7)	329 (60.9)	1.08 (0.98, 1.18)
Nausea	130 (24.0)	124 (23.0)	1.04 (0.84, 1.30)
Constipation	128 (23.6)	110 (20.4)	1.16 (0.93, 1.45)
Diarrhoea	127 (23.4)	98 (18.1)	1.29 (1.02, 1.63)
Vomiting	77 (14.2)	61 (11.3)	1.26 (0.92, 1.72)
Dyspepsia	60 (11.1)	29 (5.4)	2.06 (1.34, 3.16)
Abdominal pain	42 (7.7)	51 (9.4)	0.82 (0.56, 1.21)
Infections and infestations	305 (56.3)	212 (39.3)	1.43 (1.26, 1.63)

Upper respiratory tract infection	72 (13.3)	43 (8.0)	1.67 (1.17, 2.39)
Nasopharyngitis	60 (11.1)	45 (8.3)	1.33 (0.92, 1.92)
Urinary tract infection	51 (9.4)	41 (7.6)	1.24 (0.84, 1.84)
Bronchitis	30 (5.5)	16 (3.0)	1.87 (1.03, 3.39)
Sinusitis	28 (5.2)	6 (1.1)	4.65 (1.94, 11.14)
Influenza	27 (5.0)	18 (3.3)	1.49 (0.83, 2.68)
Vascular disorders	253 (46.7)	183 (33.9)	1.38 (1.19, 1.60)
Hot flush	123 (22.7)	99 (18.3)	1.24 (0.98, 1.57)
Hypertension	118 (21.8)	73 (13.5)	1.61 (1.23, 2.10)
Nervous system disorders	240 (44.3)	210 (38.9)	1.14 (0.99, 1.31)
Headache	74 (13.7)	66 (12.2)	1.12 (0.82, 1.52)
Dizziness	72 (13.3)	74 (13.7)	0.97 (0.72, 1.31)
Metabolism and nutrition disorders	235 (43.4)	222 (41.1)	1.05 (0.92, 1.21)
Hypokalaemia	93 (17.2)	69 (12.8)	1.34 (1.01, 1.79)
Hyperglycaemia	47 (8.7)	43 (8.0)	1.09 (0.73, 1.62)
Anorexia	40 (7.4)	38 (7.0)	1.05 (0.68, 1.61)
Decreased appetite	33 (6.1)	32 (5.9)	1.03 (0.64, 1.65)
Respiratory, thoracic and mediastinal disorders	213 (39.3)	181 (33.5)	1.17 (1.00, 1.37)
Cough	98 (18.1)	74 (13.7)	1.32 (1.00, 1.74)
Dyspnoea	68 (12.5)	55 (10.2)	1.23 (0.88, 1.72)
Injury, poisoning and procedural complications	195 (36.0)	151 (28.0)	1.29 (1.08, 1.53)
Contusion	74 (13.7)	50 (9.3)	1.47 (1.05, 2.07)
Fall	35 (6.5)	21 (3.9)	1.66 (0.98, 2.81)
Renal and urinary disorders	194 (35.8)	159 (29.4)	1.22 (1.02, 1.44)
Haematuria	60 (11.1)	31 (5.7)	1.93 (1.27, 2.93)
Pollakiuria	55 (10.1)	55 (10.2)	1.00 (0.70, 1.42)
Nocturia	34 (6.3)	28 (5.2)	1.21 (0.74, 1.97)
Urinary incontinence	34 (6.3)	25 (4.6)	1.35 (0.82, 2.24)
Investigations	190 (35.1)	145 (26.9)	1.31 (1.09, 1.56)
Alanine aminotransferase increased	65 (12.0)	27 (5.0)	2.40 (1.56, 3.70)
Aspartate aminotransferase increased	60 (11.1)	26 (4.8)	2.30 (1.47, 3.59)
Weight decreased	38 (7.0)	26 (4.8)	1.46 (0.90, 2.36)
Weight increased	28 (5.2)	39 (7.2)	0.72 (0.45, 1.15)
Skin and subcutaneous tissue disorders	180 (33.2)	146 (27.0)	1.23 (1.02, 1.47)
Rash	46 (8.5)	21 (3.9)	2.18 (1.32, 3.61)
Psychiatric disorders	144 (26.6)	123 (22.8)	1.17 (0.95, 1.44)
Insomnia	79 (14.6)	62 (11.5)	1.27 (0.93, 1.73)
Anxiety	28 (5.2)	23 (4.3)	1.21 (0.71, 2.08)
Depression	27 (5.0)	19 (3.5)	1.42 (0.80, 2.52)
Cardiac disorders	94 (17.3)	80 (14.8)	1.17 (0.89, 1.54)
Atrial fibrillation	26 (4.8)	27 (5.0)	0.96 (0.57, 1.62)
Blood and lymphatic system disorders	80 (14.8)	68 (12.6)	1.17 (0.87, 1.58)
Anaemia	61 (11.3)	52 (9.6)	1.17 (0.82, 1.66)

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
[a]Calculated using http://www.hutchon.net/confidrr.htm. Values in bold indicate statistically significant results.
AAP, abiraterone acetate plus prednisone/prednisolone; AE, adverse event; CI, confidence interval; PP, placebo plus prednisone; RR, relative risk.

Grade 3 or 4 AEs reported in ≥1% of patients in either group are summarised in Table 27. The most frequently reported grade 3 or 4 AEs were hypertension, back pain, and increased alanine aminotransferase (ALT). AAP resulted in significantly more grade 3 or 4 increased ALT, increased aspartate aminotransferase, and dyspnoea; but less hydronephrosis.

Table 27: Incidence of grade 3 or 4 AEs occurring in ≥1% of patients across randomised groups (COU-AA-302 study third interim analysis, 55% data cut-off)

System organ/class/AEs, n (%)	AAP (N=542)	PP (N=540)	RR[a] (95% CI)
Total	267 (49.3)	235 (43.5)	1.13 (1.00, 1.29)
Metabolism and nutrition disorders	61 (11.3)	42 (7.8)	1.45 (1.00, 2.10)
Hyperglycaemia	14 (2.6)	11 (2.0)	1.27 (0.58, 2.77)
Hypokalaemia	14 (2.6)	10 (1.9)	1.39 (0.63, 3.11)
Hyponatraemia	9 (1.7)	8 (1.5)	1.12 (0.44, 2.88)
Dehydration	7 (1.3)	3 (0.6)	2.32 (0.60, 8.94)
Anorexia	6 (1.1)	1 (0.2)	5.98 (0.72, 49.49)
Hypophosphataemia	5 (0.9)	7 (1.3)	0.71 (0.23, 2.23)
Investigations	51 (9.4)	27 (5.0)	1.88 (1.20, 2.95)
Alanine aminotransferase increased	30 (5.5)	4 (0.7)	7.47 (2.65, 21.07)
Aspartate aminotransferase increased	17 (3.1)	5 (0.9)	3.39 (1.26, 9.12)
Blood alkaline phosphatase increased	6 (1.1)	5 (0.9)	1.20 (0.37, 3.89)
Musculoskeletal and connective tissue disorders	48 (8.9)	60 (11.1)	0.80 (0.56, 1.14)
Back pain	15 (2.8)	21 (3.9)	0.71 (0.37, 1.37)
Arthralgia	10 (1.8)	10 (1.9)	1.00 (0.42, 2.37)
Bone pain	7 (1.3)	11 (2.0)	0.63 (0.25, 1.62)
Musculoskeletal pain	7 (1.3)	6 (1.1)	1.16 (0.39, 3.44)
Muscular weakness	3 (0.6)	6 (1.1)	0.50 (0.13, 1.98)
Infections and infestations	43 (7.9)	35 (6.5)	1.22 (0.80, 1.88)
Urinary tract infection	9 (1.7)	3 (0.6)	2.99 (0.81, 10.98)
Pneumonia	7 (1.3)	4 (0.7)	1.74 (0.51, 5.92)
Nervous system disorders	36 (6.6)	23 (4.3)	1.56 (0.94, 2.60)
Syncope	9 (1.7)	6 (1.1)	1.49 (0.54, 4.17)
Vascular disorders	36 (6.6)	31 (5.7)	1.16 (0.73, 1.84)
Hypertension	23 (4.2)	17 (3.1)	1.35 (0.73, 2.49)
Deep vein thrombosis	8 (1.5)	6 (1.1)	1.33 (0.46, 3.80)
Renal and urinary disorders	31 (5.7)	28 (5.2)	1.10 (0.67, 1.81)
Haematuria	7 (1.3)	4 (0.7)	1.74 (0.51, 5.92)
Urinary retention	7 (1.3)	3 (0.6)	2.32 (0.60, 8.94)
Hydronephrosis	1 (0.2)	8 (1.5)	0.12 (0.02, 0.99)
General disorders and administration site conditions	30 (5.5)	33 (6.1)	0.91 (0.56, 1.46)
Fatigue	13 (2.4)	10 (1.9)	1.30 (0.57, 2.93)
General physical health deterioration	6 (1.1)	2 (0.4)	2.99 (0.61, 14.74)
Asthenia	1 (0.2)	7 (1.3)	0.14 (0.02, 1.15)
Cardiac disorders	28 (5.2)	13 (2.4)	2.15 (1.12, 4.10)
Atrial fibrillation	9 (1.7)	5 (0.9)	1.79 (0.60, 5.32)
Gastrointestinal disorders	28 (5.2)	25 (4.6)	1.12 (0.66, 1.89)
Diarrhoea	6 (1.1)	5 (0.9)	1.20 (0.37, 3.89)
Abdominal pain	3 (0.6)	9 (1.7)	0.33 (0.09, 1.22)
Respiratory, thoracic and mediastinal disorders	28 (5.2)	23 (4.3)	1.21 (0.71, 2.08)
Dyspnoea	14 (2.6)	5 (0.9)	2.79 (1.01, 7.69)
Pulmonary embolism	11 (2.0)	15 (2.8)	0.73 (0.34, 1.58)
Blood and lymphatic system disorders	21 (3.9)	19 (3.5)	1.10 (0.60, 2.02)
Anaemia	13 (2.4)	10 (1.9)	1.30 (0.57, 2.93)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	20 (3.7)	22 (4.1)	0.91 (0.50, 1.64)
Cancer pain	5 (0.9)	9 (1.7)	0.55 (0.19, 1.64)

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
[a]Calculated using http://www.hutchon.net/confidrr.htm. Values in bold indicate statistically significant results.

AAP, abiraterone acetate plus prednisone/prednisolone; AE, adverse event; CI, confidence interval; PP, placebo plus prednisone; RR, relative risk.

AEs of special interest (as described in the EPAR for AA) include events related to mineralocorticoid excess (hypertension, hypokalaemia, and fluid retention), cardiac disorders, and hepatotoxicity. These AEs were reported in a higher proportion of patients in the AAP group than in the PP group (68.6% vs. 51.3%; Table 28).

The most commonly reported subcategories of AEs of special interest were fluid retention (29% AAP vs. 24% PP), hypertension (22% vs. 14%), cardiac disorders (21% vs. 18%), hepatotoxicity (19% vs. 11%), and hypokalaemia (17% vs. 13%). The incidence of grade 3 and above events was <10% for all individual special events (Table 28).

Table 28: Incidence of AEs of special interest (>5% in either arm) (COU-AA-302 study third interim analysis, 55% data cut-off)

n (%)	**AAP (N=542)**					**PP (N=540)**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
AE of special interest	151 (27.9)	109 (20.1)	97 (17.9)	11 (2.0)	3 (0.6)	130 (24.1)	81 (15.0)	57 (10.6)	6 (1.1)	3 (0.6)
Fluid retention/oedema	116 (21.4)	37 (6.8)	5 (0.9)	0	0	85 (15.7)	36 (6.7)	8 (1.5)	1 (0.2)	0
Peripheral oedema	107 (19.7)	31 (5.7)	2 (0.4)	0	0	75 (13.9)	33 (6.1)	5 (0.9)	0	0
Hypertension	46 (8.5)	49 (9.0)	23 (4.2)	0	0	27 (5.0)	29 (5.4)	17 (3.1)	0	0
Cardiac disorders	46 (8.5)	28 (5.2)	32 (5.9)	4 (0.7)	3 (0.6)	38 (7.0)	35 (6.5)	16 (3.0)	3 (0.6)	3 (0.6)
Arrythmias	38 (7.0)	19 (3.5)	18 (3.3)	3 (0.6)	1 (0.2)	33 (6.1)	24 (4.4)	11 (2.0)	0	2 (0.4)
Hepatotoxicity	25 (4.6)	34 (6.3)	38 (7.0)	5 (0.9)	0	30 (5.6)	16 (3.0)	13 (2.4)	2 (0.4)	0
ALT increased	14 (2.6)	21 (3.9)	27 (5.0)	3 (0.6)	0	18 (3.3)	5 (0.9)	3 (0.6)	1 (0.2)	0
AST increased	24 (4.4)	19 (3.5)	17 (3.1)	0	0	13 (2.4)	8 (1.5)	5 (0.9)	0	0
Hypokalaemia	74 (13.7)	5 (0.9)	12 (2.2)	2 (0.4)	0	59 (10.9)	0	10 (1.9)	0	0

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AAP, abiraterone acetate plus prednisone/prednisolone; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PP, placebo plus prednisone/prednisolone.

The incidence rates of selected AEs were also studied by duration of exposure [72]. There was no clinically relevant increase in the incidence rate of AEs with longer exposure of AAP compared with PP (appendix 14 [section 10.14.4]).

Treatment-emergent adverse events (TEAEs) of special interest standardised for the duration of treatment exposure are shown in Table 29. The only individual TEAEs of special interest with a difference ≥5 events/100 patient years were increases in ALT and AST.

Table 29: TEAEs of special interest with event rates ≥5 per 100 patient years of exposure in either group (COU-AA-302 study third interim analysis, 55% data cut-off, Safety Population)

AE of interest (preferred term)	**AAP (N=707.5)**	**PP (N=495.0)**
Number of distinct TEAEs of special interest	1,144 (161.7)	717 (144.8)
Fluid retention/oedema	264 (37.3)	214 (43.2)
Oedema peripheral	229 (32.4)	177 (35.8)

Hypokalaemia	158 (22.3)	105 (21.2)
Hypertension	158 (22.3)	96 (19.4)
Hepatotoxicity	363 (51.3)	148 (29.9)
ALT increased	156 (22.0)	42 (8.5)
AST increased	109 (15.4)	37 (7.5)
Blood alkaline phosphatase increased	38 (5.4)	34 (6.9)
Cardiac disorders	201 (28.4)	154 (31.1)
Arrhythmias	116 (16.4)	97 (19.6)
Atrial fibrillation	33 (4.7)	35 (7.1)
Ischaemic heart disease	35 (4.9)	29 (5.9)
Cardiac disorders for other causes	26 (3.7)	26 (5.3)

AAP, abiraterone acetate plus prednisone/prednisolone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PP, placebo plus prednisone/prednisolone; TEAE, treatment-emergent adverse event.

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

As shown in the pivotal COU-AA-302 study, the safety profile of AAP is generally acceptable, and AEs that do occur are usually manageable with basic medical interventions (e.g. analgesics, anti-hypertensive agents, potassium supplements, aldosterone antagonists, diuretics). Of particular note, individual grade 3/4 AEs of special interest (hypertension, hypokalaemia, fluid retention/oedema, cardiac disorders, and hepatotoxicity) were relatively low and did not occur in more than 5.5% of patients who received AAP.

The AEs associated with AAP do not represent a substantial additional burden compared to PP; this is especially important in the treatment of asymptomatic or mildly symptomatic patients for whom an intervention with many severe AEs would not be appropriate. It should be noted that the CHMP Assessment Report for AA in the post-ADT, pre-chemotherapy setting concluded that ‘treatment with abiraterone was tolerable for the majority of subjects and the safety profile was generally consistent with previous experience, although exposure to the drug was significantly longer than in previous studies. AEs were manageable and no major safety concerns have been raised for this application and indication’ based on the results of the COU-AA-302 study [16]. Furthermore, that the ‘favourable effects are considered to more than exceed the unfavourable effects/uncertainties and overall the benefit risk profile is considered to be positive’ [16].

6.10 Interpretation of clinical evidence

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

The primary clinical objectives of treating mCRPC (as noted in the earlier NICE STA submission for AAP for the treatment of mCRPC following previous cytotoxic therapy [61]) are to prolong survival, delay disease progression, and maintain patients’ quality of life (QoL) for as long as possible. As shown in section 6.5, AAP demonstrated benefits in these key outocmes consistently in patients with asymptomatic or mildly symptomatic mCRPC in whom ADT had failed and chemotherapy was not yet clinically indicated. AA is the first drug that has been

robustly studied in, and specifically licensed for, this patient population, and thus fulfils an unmet need. In COU-AA-302, AAP was generally well tolerated and rarely associated with debilitating AEs (section 6.9) that compromised QoL. In addition, patients experienced slower deteriorations in physical, emotional, and functional wellbeing as assessed via the FACT-P (section 6.5.3).

The primary clinical benefit of AAP was that it significantly improved median rPFS vs. PP: 16.5 (95% CI [redacted]) vs. 8.2 (95% CI [redacted]) months (HR=0.52, p<0.0001). AAP also improved median OS: 35.3 (95% CI 31.2, 35.3) vs. 30.1 (95% CI 27.3, 34.1) months (HR=0.79, p=0.0151). Although this result at the third interim analysis did not reach the pre-specified significance boundary of p=0.0034, the trial had been stopped by the IDMC prior to this point due to a 'highly significant advantage' for patients at the second interim analysis in the AAP arm. Furthermore, the EMA concluded that 'The most influential factors for a positive opinion are the magnitude in the delay of progression and the clinically relevant advantage of the delay in time to initiation of chemotherapy and reduced opiate use' [16].

Pain is a debilitating problem in patients with mCRPC with bone metastases and is a prognostic factor for survival [44;88]. Also, patient-reported outcomes more accurately reflect patients' perception of a disease and its treatment [89]. The progression of pain and HRQL were both noted to be important outcomes to be considered in the treatment of patients with mCRPC by the consultees and commentators in the final scoping for this appraisal [90;91]. Both the BPI and FACT-P instruments used in the COU-AA-302 study are validated instruments for prostate cancer. The results of the study show that patients who received AAP were more likely to experience slower worsening of physical, emotional, and functional wellbeing and have more time before their pain worsened and their ECOG PS deteriorated than patients who received PP. These findings constitute clear evidence of a meaningful clinical benefit for patients who receive AAP.

AEs associated with taking AAP were mild to moderate in nature, and generally manageable with basic medical interventions. Of note, the incidence of individual grade 3 or 4 AEs was relatively low and did not exceed 6% in the AAP arm of the study.

AA has been developed to target the second leading cause of cancer death in men in the UK; prostate cancer deaths account for 12.5% of all male cancer mortality [92]. AA is a novel, first in class, oral therapy that inhibits testosterone production at all three key sites in patients with prostate cancer (tumour, testes, and adrenal glands). The novel mechanism of action and clinical outcomes observed with AA have necessitated the creation of a separate category within the LO2BX class of agents by the WHO International Working Group for Drug Statistics Methodology; the new ATC code assigned is L02BX03 'Other hormone antagonists and related agents'.

The results of the COU-AA-302 study also indicate that treatment with AAP is aligned to meet objectives set by the National Health Service (NHS) Outcomes Framework [93], specifically:

- Domain 1: Preventing people from dying prematurely. Results from the third interim OS analysis showed a 21% reduction in the risk of death with AAP vs. PP. While this result was not statistically significant for the reasons outlined in

section 6.5.3, the trial was stopped prematurely by the IDMC based on a 25% reduction in the risk of death at the second interim analysis.

- Domain 4: Ensuring that people have a positive experience of care. AA is administered orally and can be taken at home; this can ensure care closer to home for prostate cancer patients in an advanced disease setting. Moreover, it delayed the development of pain and worsening of HRQL.

In summary, AAP offers patients with asymptomatic or mildly symptomatic mCRPC an oral treatment option that increases their life expectancy and delays disease progression without compromising HRQL. Moreover, given the existing funding arrangements for AAP in the post-chemotherapy setting, these results in the pre-chemotherapy setting present clinicians with the option for earlier use of AAP without having to use docetaxel first. This is key, as patients will be able to benefit from AAP prior to being exposed to the potential toxicities associated with docetaxel at an earlier stage of their disease, when they are fitter and healthier.

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

A single pivotal Phase III study, COU-AA-302, has been conducted to assess and compare the efficacy and safety of AAP. This high-quality study was robust in terms of efficacy and safety outcomes, and is relevant to the decision problem. The design of the study was finalised following advice and input from the FDA and CHMP. The COU-AA-302 study was considered to be adequate to support authorisation, with statistically compelling and clinically relevant results, by the EMA [16].

As discussed in sections 1.6, 6.3.2, 6.3.8, 6.5.3, and 6.10.1, the trial was halted early by the IDMC due to a ‘highly significant advantage’ for patients on AAP, even though the stringent pre-specified level of statistical significance for OS had not been reached.

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

The pivotal Phase III clinical study (COU-AA-302) is directly related to the decision problem as this study compares AAP to the relevant comparator of PP (i.e. a corticosteroid plus supportive care, i.e. a form of BSC) in the patient population of interest. The outcomes assessed in the clinical study are based on established parameters including rPFS, OS and HRQL (as measured via the FACT-P). Therefore these outcomes reflect the clinical benefits important to the patient population of interest. Additional outcomes assessed in the COU-AA-302 study included parameters such as time to pain progression, time to analgesic progression, and time to cytotoxic chemotherapy. These are relevant in clinical practice and in managing the disease.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the

technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Given the disease that has been studied, the nature of the established parameters studied, and the robustness of the outcomes, Janssen does not anticipate that the study results observed in the clinical studies will differ from those that will be observed when using AAP in clinical practice within the NHS. The dose of AA used in the clinical study (and in the SPC) is identical to the dose that will be used in clinical practice in England and Wales.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

An update to the systematic review used in the earlier NICE STA submission for AA for the treatment of mCRPC following previous cytotoxic therapy was conducted to identify all primary studies in mCRPC that involved an economic evaluation, a burden of illness study, or an evaluation linked to a Health technology assessment (HTA) submission [61].

Literature databases (MEDLINE© [including MEDLINE© In-process, Other Non-Indexed Citations], Excerpta Medica Database [Embase©], Cochrane© [NHS EED, Technology Assessments databases; CENTRAL, EconLit©) were searched to identify studies published between 01.01.00 and 02.09.13. Standard filters based on those developed by the Scottish Intercollegiate Guidance Network were used to identify economic studies in MEDLINE© and Embase© [94]. Clinical keywords and medical subject headings were used to search for disease and interventions, and these are fully explained in appendix 10 (section 0). To supplement the review, conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and ISPOR European conferences (2006–2012) were hand searched; as were HTA websites (UK, US, Australia, Canada, Global). To be included in the review, studies had to meet pre-defined eligibility criteria specified in the systematic review protocol. Only English language studies were included. Inclusion criteria for the review are detailed in Table 30.

Table 30: Inclusion criteria for the economic evaluations systematic review

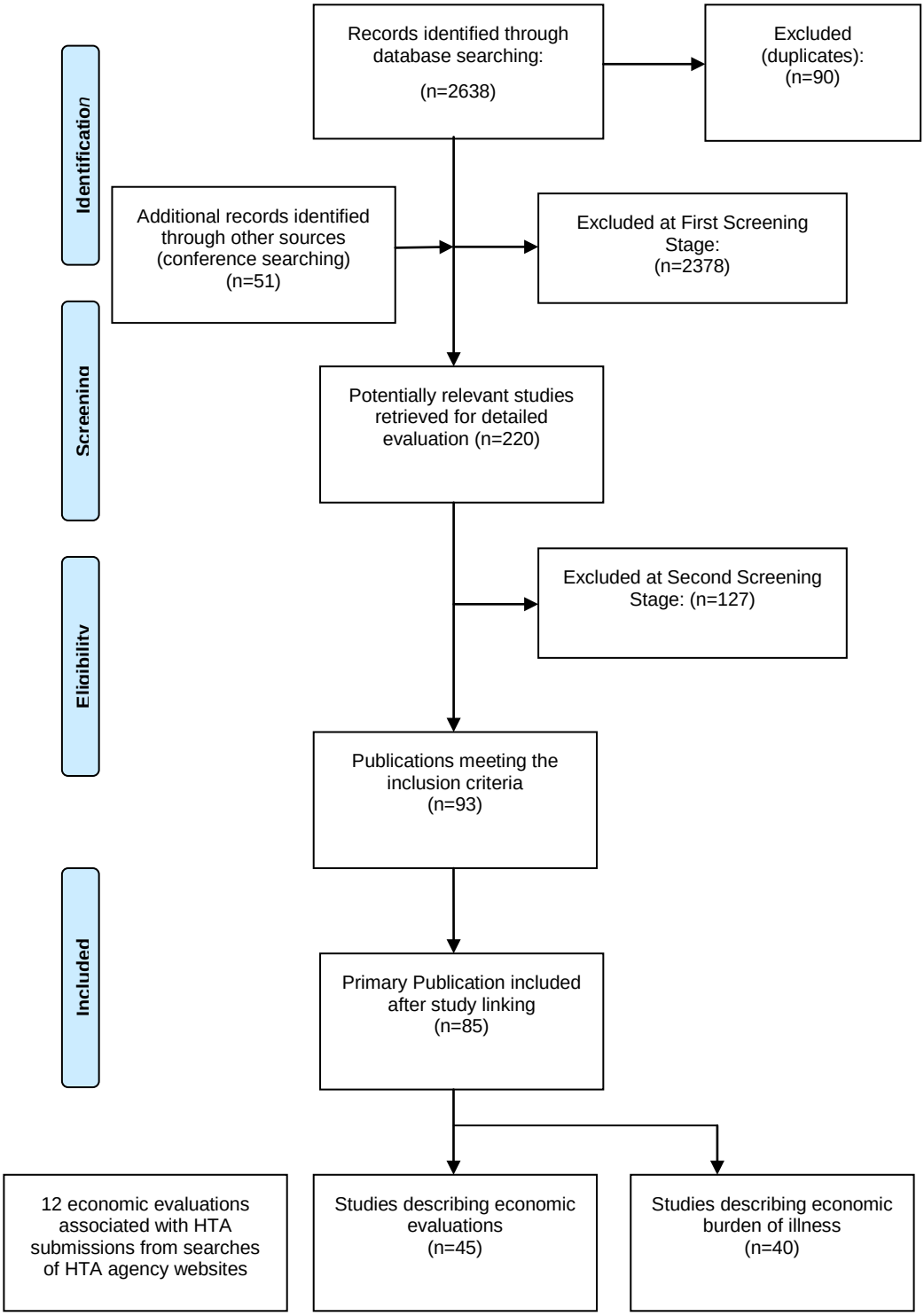
Studies to include		Rationale
Study designs	Budget impact analyses, Resource use studies, Cost/economic burden of illness studies, Cost analyses, Cost-minimisation analyses, Cost-effective analyses, Cost-utility analyses, Cost-benefit analyses, Clinical trial-based analyses	These types of economic studies were seen as 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		The restriction would not limit results substantially due to data availability in English language

5-FU, 5-fluorouracil; CAB, combined androgen blockade; mCRPC, metastatic castration-resistant prostate cancer.

Bibliographic details and abstracts of all citations identified by the literature search were downloaded into a bespoke, Structured Query Language (SQL)-based internet database. Citations were first screened by a single reviewer based on the abstract supplied with each citation. Those that did not meet 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. In instances where 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. The data presented in the studies still included after this stage were extracted to data-extraction grids. This stage involved a single reviewer with decisions and extractions checked by a second reviewer [56].

Figure 9: Trial flow diagram for the systematic review of relevant cost-effectiveness studies



HTA, health technology assessment.

Description of identified studies

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

The systematic literature review identified 45 economic evaluations [95-139] and 12 additional economic evaluations associated with HTA appraisals [15;45;140-149]. None of the studies identified investigated AAP for the treatment of adult men who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated.

The details of the studies identified by the literature search (excluding studies of antiandrogens, LHRHs, and drugs to protect against skeletal problems) are described in Table 140 (appendix 15). Similarly, details of economic evaluations included as part of HTA appraisals are described in Table 141 (appendix 15).

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

N/A, as no studies directly relevant to the decision problem were identified.

7.2 De novo analysis

Patients

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

The target population for treatment with AAP is in adult men who are asymptomatic or mildly symptomatic mCRPC after failure of ADT in whom chemotherapy is not yet clinically indicated. The population included in the model, as an approximation of the UK target population, is closely based on the COU-AA-302 trial (Table 31) [65]. All

[1] 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.

[2] 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.

patients had previously been treated with hormonal therapy, 54.0% had received prior radiotherapy, and 46.0% prior surgical therapy. The use of anti-androgen therapies, including bicalutamide, nilutamide, flutamide, and azole drugs, was prohibited during the trial period [18].

Table 31: Characteristics of patients in the COU-AA-302 trial

Characteristic	AAP (N=546)	PP (N=542)	Overall (N=1,088)
Age, years, median	71	70	70
Male, %	100	100	100
Race, %			
White	95.4	94.4	94.9
Black	2.8	2.4	2.6
Asian	0.7	1.7	1.2
Native Hawaiian / Other Pacific Islander	0	0.4	0.2
Other	1.1	1.1	1.1
Time from diagnosis to first dose, years	6.7	6.5	6.6
Alkaline phosphatase, IU/L, median	93.0	90.0	91.0
Haemoglobin, g/dL, median)	13.0	13.1	13.1
Lactate dehydrogenase, IU/L, median	187.0	184.0	185.0
Baseline serum PSA, ng/mL			
Median	42.0	37.7	39.5
Range	0–3,927	1–6,606	0–6,606
BPI-SF #3 pain score, %			
0–1	68.6	64.8	66.7
2–3	23.9	27.5	25.7
≥4	7.4	7.7	7.5
Bone metastasis, %	83.1	79.7	81.4

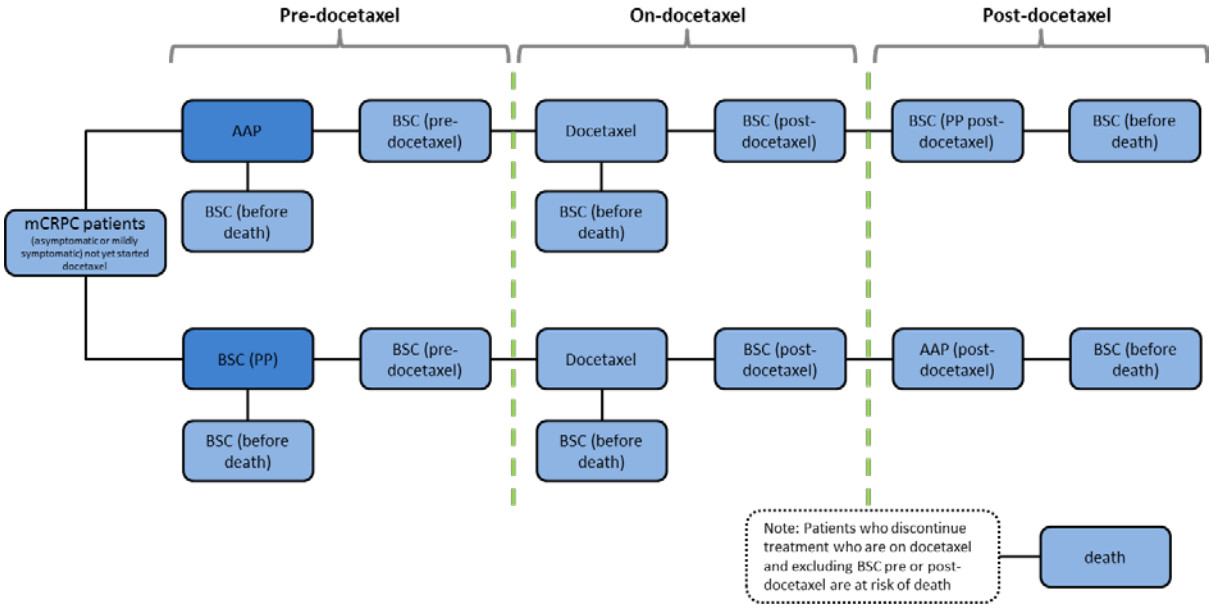
SOURCE: COU-AA-302 study clinical study report (unpublished) [65].
AAP, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory – short form; IU, international units; PP, placebo plus prednisolone/prednisone; PSA, prostate-specific antigen.

Model structure

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

The model adopts a treatment pathway structure, simulating multiple courses of therapy from the start of AAP/BSC (PP) until death (Figure 10). The pathway structure allows for the tracking of subsequent treatments after discontinuation from AAP and conceptualises the course of mCRPC better than the conventional three-health-state structure of PFS, post-progression, and death (NICE TA259), which oversimplifies the disease clinical pathway after patients discontinue from AAP.

Figure 10: Model pathway



AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.
The size of the boxes does not reflect active treatment/BSC duration.
Patients only receive licensed products or those with positive reimbursement appraisal.

The model evaluates the cost-effectiveness of AAP in comparison to BSC (PP) in adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. The comparator, BSC (PP), is a proxy for an active monitoring strategy based on the PP group in the COU-AA-302 trial (please see section 7.2.7 for a detailed description on the selection of comparators).

A UK advisory board in November 2012 [55] indicated that it was appropriate to use the control arm of the trial (i.e. prednisolone with placebo) to reflect an active monitoring strategy. Note that dexamethasone is a commonly used corticosteroid in the UK [55], and the model assumes that it has similar efficacy to prednisolone plus placebo in the COU-AA-302 trial. Although the various phases in the treatment pathway outwardly mirror similar descriptions in the naming convention (e.g. BSC [PP], BSC [pre-chemotherapy], etc.), each phase actually represents a discrete element of the patient pathway.

Importantly, if treatment phases were merged under one depiction, for example, BSC, or any of the identified phases were removed from the treatment pathway, it would be assumed that patients spend zero time in this phase and the model would therefore not be able to replicate the COU-AA-302 trial results or AAP's relative benefit.

In the COU-AA-302 trial, where data on subsequent treatments received was collected while patients remained alive, the treatment pathway was similar to the model structure presented in Figure 10, but patients could go on to receive post-docetaxel active treatment (e.g. cabazitaxel). However, since this drug is not NICE-approved in the UK, in the model, patients could only receive post-docetaxel BSC (or

AAP if they had not received post-ADT AAP). Table 32 contains a summary of the treatment phases included in the model.

Table 32: Summary of treatment phases

Treatment phase	Description
AAP, BSC (PP) and docetaxel	Time on active treatment
BSC pre-/post-docetaxel	Time before receiving an active treatment that has been shown to impact overall survival. Patients are still receiving treatments that palliate symptoms of disease
BSC (before death)	End-of-life phase where patients are near death and will not receive additional active treatments that may impact survival, but instead are managed for their pain or other symptoms

Patients diagnosed with asymptomatic or mildly symptomatic mCRPC post-ADT entered the model and were assigned to one of the two treatment pathways. Current clinical practice in the UK follows the lower of the two model treatment arms in Figure 10 and involves monitoring and BSC until a patients' disease and symptoms have progressed sufficiently for the clinician to consider commencing treatment with docetaxel. The upper pathway of Figure 10 represents the UK treatment sequence modified to incorporate the use of AAP treatment post-ADT when a patient is still asymptomatic or mildly symptomatic.

After the pre-docetaxel treatment is discontinued, or disease progression occurs, patients are monitored in a BSC (pre-docetaxel) phase prior to commencing docetaxel treatment. Those patients who are considered unsuitable for docetaxel treatment (i.e. Karnofsky PS ≥60% [147], which is approximately ECOG PS <2) transition to BSC in the model and receive no further active treatment prior to death.

After docetaxel treatment is completed, patients are again monitored for disease progression. When progression occurs, a patient can receive further active treatment if the benefits outweigh the risks (i.e. the predicted use of post-docetaxel active treatment is based on the observations from the COU-AA- 302 trial. Accordingly, active treatments could include enzalutamide and cabazitaxel. In this submission, the predicted use of post-docetaxel treatment is restricted to BSC).

Finally, it is assumed that, after all treatment options have been explored and the disease is progressing, BSC would evolve into an approach involving palliative care, until death. The BSC post-docetaxel phase aims to capture the slow progression of the disease during which time patients receive treatments to alleviate worsening symptoms. If patients received AAP prior to docetaxel it is assumed they would not be eligible for AAP retreatment post-docetaxel. Conversely, eligible patients in the comparator arm (BSC [PP]) may receive AAP post-docetaxel. BSC (before death) represents the end stage of life due to the severity of illness rendering patients unsuitable for additional active treatment. Feedback from expert clinical opinion indicates that the aforementioned pathway is representative of current UK clinical practice [54;55]. It is also in line with NICE [2] treatment guidelines.

The model structure permits the start and end of treatments that impact on survival to be tracked. Patients may receive other treatments, but these are not expected to impact survival (i.e. no evidence exists demonstrating a statistically significant impact

on survival) and are not explicitly tracked in the model. The BSC phases pre- and post-docetaxel capture the time once the first treatment is discontinued and before docetaxel starts and the time of docetaxel discontinuation to start of the post-docetaxel active treatment. Patients in these phases can still receive other subsequent treatments, but not docetaxel or AAP, the rationale for this being:

- Patients can receive palliative treatments before docetaxel such as steroids, mitoxantrone, axitinib, capecitabine, etc. (as seen in the COU-AA-302 trial). For BSC (pre-docetaxel) in the BSC (PP) arm, this reflects patients who may continue on the same treatments, or receive other medications from the list above, but have experienced signs of progression and perhaps some change to their management
- Patients are unlikely to start docetaxel the same week they finish AAP or BSC (PP). Based on discussions with key opinion leaders (KOLs), from the end of one treatment to a subsequent active treatment, time is required for a work-up and scheduling of infusion visits that take some time
- A patient's or physician's preference is to give patients a rest between active treatments (based on discussions with KOLs.

Treatment pathway model overview

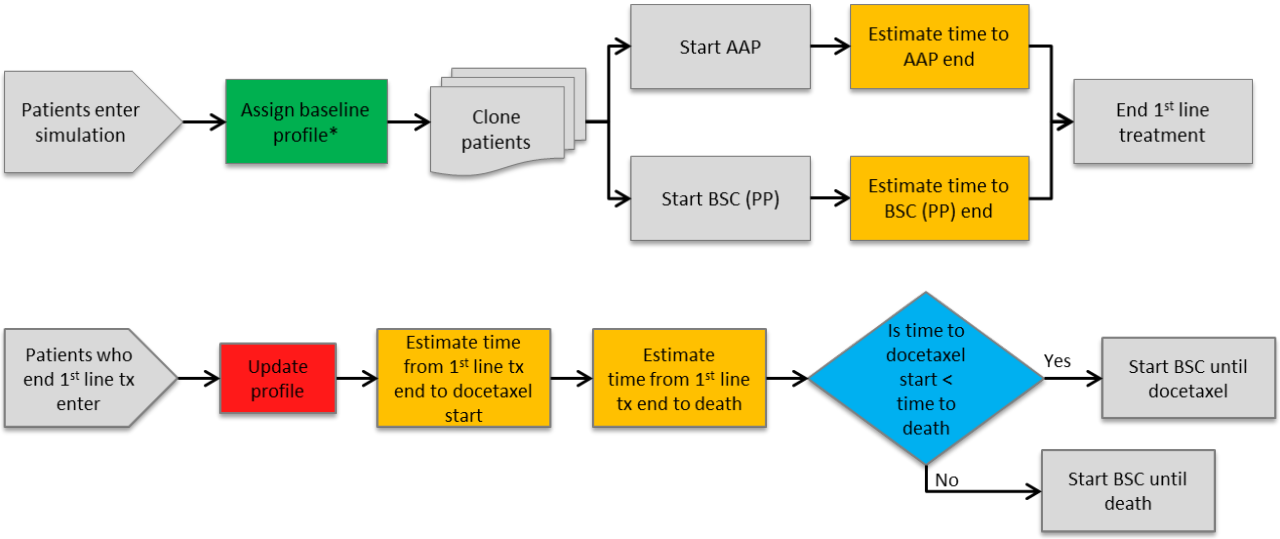
The model approach uses an individual time-to-event simulation or DES in its simplest form to track patients and their treatment experiences at the individual level. The rationale for the model approach is provided in section 7.2.3).

Figure 11 depicts the patient flow through the three phases (pre-docetaxel, docetaxel, post-docetaxel) of the model. First, in the pre-docetaxel phase (Figure 11A), patients with mCRPC (asymptomatic or mildly symptomatic) are assigned a baseline profile, and the profiles were duplicated to allow patients with the same characteristics to progress through treatment arms (AAP and BSC [PP]). When patients finished AAP or BSC (PP) treatment, their profiles (e.g. age, ECOG score) were updated, and times to docetaxel start and to death were estimated. If the estimated time to docetaxel start was less than time to death, a patient received docetaxel and their estimated time to docetaxel determined the duration of BSC (before docetaxel). Otherwise, patients moved to BSC (before death) until death.

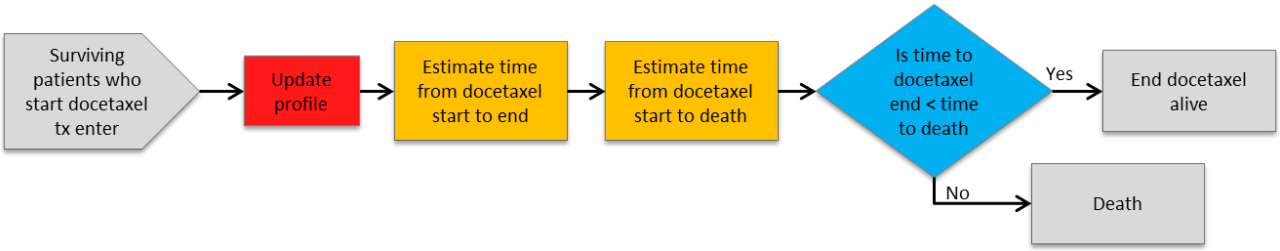
Patient profiles were updated at the start of docetaxel treatment (Figure 11B). Times from docetaxel start to treatment end and to death were estimated. Patients could die during treatment with docetaxel (i.e. time to docetaxel end was longer than time to death) or fail docetaxel treatment alive. The latter group's profiles were updated at docetaxel discontinuation, and so was their time to death (Figure 11C). Time to post-docetaxel treatment was estimated and compared with time to death. Patients whose time to death was less than time to next treatment moved on to BSC until death, while the others received post-docetaxel treatment after a period of time receiving BSC. These patients had their profiles updated upon starting the next treatment, and their times to treatment discontinuation and from treatment discontinuation to death were estimated. The simulation terminated when the patient died or the analysis time horizon was reached (up to age 100).

Figure 11: Patient flow through the simulation

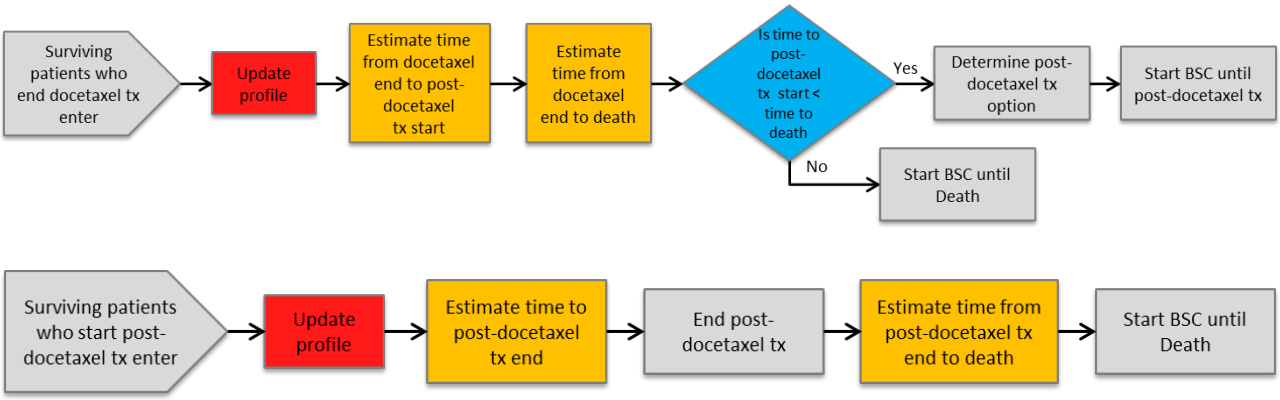
A



B



C



Baseline patient profiles

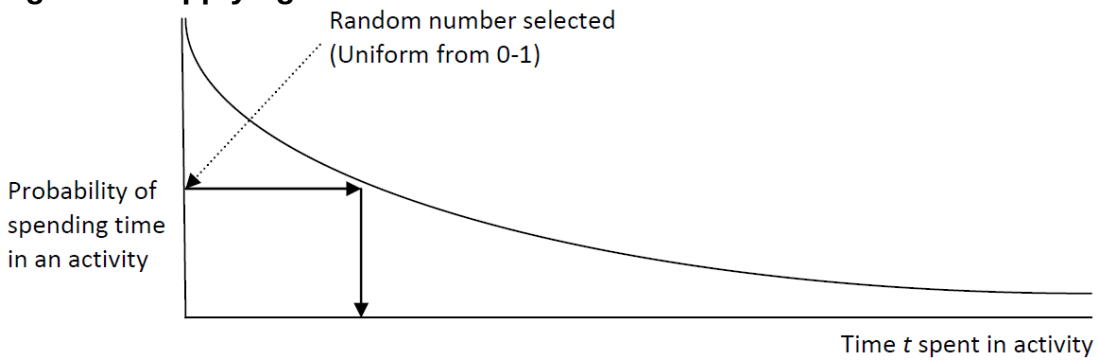
Baseline profiles were created for each patient with mCRPC (asymptomatic or mildly symptomatic) whose treatment course was simulated. Each patient profile contained information on demographic and clinical/disease-related characteristics (e.g. age, BMI, time since diagnosis, ECOG). Characteristics were sampled directly from the observed data of patients in the COU-AA-302 trial, maintaining the within-patient correlations of the characteristics. The approach for sampling patient characteristics is selectable (see section 7.6.1). Each patient profile was cloned (i.e. profiles with the same baseline characteristics are generated) to predict pathways of individual patients with identical profiles in each treatment arm. Patients were simulated over

time in a specific treatment pathway dependent on their characteristics (e.g. BMI, age), predicted disease status (e.g. ECOG), and treatment experience (e.g. time spent with previous treatments).

Estimate time between events

The simulation model estimated the time spent in each phase using prediction equations. These periods were determined by survival curves and were assumed to follow a specified parametric distribution (Weibull, exponential, log-logistic, or lognormal) based on the corresponding prediction equation. The curve was used to translate a random number to the time spent in an activity. A uniformly distributed (from 0 to 1) random number was generated and applied to the inverse of the survival function yielding the time spent in each specific part of the treatment pathway. Thus, there was a particular probability (given by the random number) of spending exactly time *t* in each phase of the model (refer to Figure 12). The functions corresponding to each distribution are provided in appendix 16, along with a more detailed explanation of how the times were predicted in the simulation.

Figure 12: Applying a random number to a survival curve



Allocate cost and utility

Costs and QALYs are associated with time spent in each phase (on treatment or BSC) of the simulation model. As per NICE guidelines, all costs and QALYs were discounted at an annual rate of 3.5%. The continuous discounting function (Equation 1) was used to compute the present value (PV) of a cost C to be received T days (time activity treatment phase is terminated) from the time an activity is initiated (T_0), assuming a rate *r* of 3.5%, continuously discounted. A similar formula applied for discounting QALYs over time where the cost *C* was replaced by the health state utility value linked to the phase. Discounted costs and QALYs were estimated at the termination of each treatment phase over the time spent in it, and total costs and QALYs for patients from the start of AAP/BSC (PP) treatment were summed over time.

(Equation 1)

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

Rationale of clinical pathway

As discussed in section 7.2.2, the chosen structure is in line with UK NICE clinical guidance [2], as well as other guidance as outlined in section 2.5.

Rationale of model structure

Existing approaches for modelling advanced cancer were reviewed and the most common design was found to be a three-state Markov model using pre-progression, post-progression, and death. There are two problems with the applicability of this design for modelling the impact of introducing AAP into the mCRPC disease pathway post-ADT. First, it is an over-simplification to assume patients living with prostate cancer can only be in one of two health states; a pathway structure is more appropriate to account for multiple health states that patients experience as their disease progresses. Second, this design is unable to reflect the changes to the clinical treatment pathway that may occur with the addition of AAP as a new first-line indication post-ADT for men who would then go on to receive docetaxel, and potentially subsequent active treatments if applicable. An individual-based DES was deemed to be a more appropriate design for modelling the specificities of this treatment pathway. The events were implemented as a straightforward linearly linked list which is efficient given that the event set in the model is fairly small. Alternatively, in a DES, there may be many events in the set and a loop format is warranted. The underlying principles of DES hold under both formats.

The objective of the individual-based simulation is to model COU-AA-302 trial data and consequentially estimate effectiveness and cost-effectiveness in UK clinical practice. In a standard Markov model, PFS and OS curves would be extrapolated to obtain transition probabilities. This discrete-event simulation differs in that it utilises patient-level trial data and baseline characteristics alongside patient treatment history, to estimate a series of predictive equations in order to depict the duration of time a particular patient will spend in each treatment phase. Time dependencies were captured as patient characteristics evolve with each treatment phase and future durations depend on patient history (e.g. time on previous therapy, patient characteristics at discontinuation of prior therapy). Inevitably this is more complicated than a simple statistical extrapolation but this dynamic design has distinct advantages over a traditional Markov model as follows:

- Structure reflects clinical reality of the mCRPC treatment pathway in the UK
- Based on individual patient data from study COU-AA-302
- Results can be produced for patients with varying baseline characteristics.

The reasons for selecting an individual time-to-event simulation included:

1. Reflects mCRPC patients' treatment experience with multiple courses of therapy
    - An individual-level simulation approach makes it possible to track the multiple courses of treatments (treatment prior to docetaxel, during docetaxel and post-docetaxel) over the mCRPC disease progression pathway. The COU-AA-302 trial focuses on the use of AA in mCRPC patients who are not in immediate need of chemotherapy due to their lack of moderate-to-severe bone pain or rapid tumour progression. In current clinical practice in the UK, patients who are asymptomatic or mildly symptomatic are actively monitored and may receive supportive treatments, once they become more symptomatic they receive chemotherapy, of which the treatment of choice is docetaxel. Some surviving patients will go on to receive post-docetaxel treatments. A modelling approach that could capture a treatment pathway with multiple courses of therapy was needed. A treatment pathway structure allows for the tracking of subsequent treatments after discontinuation from AAP and

simulates the course of mCRPC more accurately than the conventional three-health-state structure of PFS, post progression, and death [2].

- A ‘time to event’ simulation is based on ‘events’ rather than mutually exclusive ‘health states’. As survival data are typically analysed to directly report ‘time to event’ equations (e.g. time to AAP discontinuation), a time to event approach is superior to the individual Markov approach that requires a conversion to time-dependent transition probabilities. In contrast to individual state transition-based models, event-based simulation captures the experience of patients (i.e. natural course of disease, treatment patterns) with more flexibility, accuracy and realism. Since time is dynamic, versus pre-defined time intervals, time between events (e.g. time on AAP) can reflect what occurs in practice with no *a priori* restrictions. This is important because it allows time dependencies that impact timing of events/duration of treatment to be implemented more appropriately. Furthermore, patient characteristics are defined at the start of the simulation and are updated at the time events occur (e.g. age increases, disease progression occurs). Individuals moved from one event to another with future event times dependent on the patient’s history (e.g. time on previous therapy, patient characteristic at AAP discontinuation). Additionally, given that the timing of events was unrestricted, ‘half-cycle’ corrections aimed to decrease the error introduced by stationary time cycles were not necessary.

2. Allows tracking of survival, resource use and QoL data over multiple courses of treatment
   - A pathway structure allowed patients to be tracked after initial treatment discontinuation and for resource use, survival, and QoL data to be assigned more appropriately than a three-health-state approach. Specifically, the pathway approach assigns the appropriate utility and costs associated with disease progression after the use of AAP or BSC (PP). The three-health-state model cannot track patient progression/treatment status and thus can only assign ‘average’ costs and utility for the post-progression state.
3. Creates flexibility for testing scenarios that reflect current UK practices
   - Several new drugs with demonstrated survival benefits in the post-docetaxel setting have become available in the last couple of years. Some of these treatments were received by patients in the COU-AA-302 trial, but may not be in use in clinical practice. The COU-AA-302 trial captured time to AAP or PP to docetaxel (secondary trial endpoint) and to other subsequent treatments. In the UK, not all of the new treatment options captured in the trial for patients with mCRPC have licensing agreements. Specifically, in the UK, cabazitaxel is not recommended by NICE for reimbursement, which limits its use in practice [45]. Further, in the UK, AAP is already recommended for post-docetaxel treatment, so a model that examines sequences that include AAP in this setting is also relevant. Additionally, since AAP demonstrates survival benefits, the modelling approach needed to be able to modify the survival curve depending on the treatments received. A pathway approach allowed for different scenarios to be evaluated on post-docetaxel drug use and those effects on the cost-effectiveness story of AAP in the pre-docetaxel phase.

Patients in the model initiated treatment with either AAP or BSC involving prednisolone (BSC [PP]); the only relevant treatment options for asymptomatic or mildly symptomatic mCRPC patients who are not yet clinically indicated for

chemotherapy (please see section 2.7 for further details).The PP arm of the COU-AA-302 study can be considered a suitable proxy for the BSC strategy used in clinical practice in the UK [55].

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

As the model was an individual time-to-event simulation model, there were no explicit health states. Using the prediction equations from the statistical analysis, a treatment pathway model was developed to simulate individual clinical experience starting from AAP or BSC (PP) through docetaxel and drugs taken after docetaxel, until death. The simulation was comprised of events (treatment start/discontinuation, death) and discrete activities (e.g. whilst on treatment), with time progressing as a set of sequential events and activities (events and activities are described in Table 33). As each event occurred at a discrete point in time, the activity was changed (e.g. on AAP to on BSC before starting docetaxel, awaiting start of docetaxel) with time advancing during the activity (which could be terminated by multiple events or if the time horizon was exhausted). Characteristics (e.g. ECOG status) of the simulated patients were applied to prediction equations to estimate time between events, as well as change in characteristics with time. The simulation kept a record of the current simulation time and time increments based on the events that occurred; i.e., as one event was completed, the clock jumped to the start time of the next event and the simulation proceeded in this fashion.

Table 33: Summary of simulation model events and activities

Event / Activity type	Description
Event	
Treatment start	Patients started active treatment
Treatment discontinuation	Patients discontinued use of active treatment
Death	Patients exited the simulation
Activity	
On treatment	Time on active treatment (e.g. AAP, BSC (PP), docetaxel)
BSC (before docetaxel, post-docetaxel)	Time before receiving an active treatment that has been shown to impact overall survival, patients were still receiving treatments that palliate symptoms of disease
BSC (before death)	End-of-life phase where patients are near death and did not receive additional active treatments that may impact survival, but instead were managed for their pain or other symptoms

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

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

The model captured key events central to the clinical treatment pathway for mCRPC, including PFS (time on AAP or BSC [PP] is a proxy for PFS), treatment duration, and OS. Other key aspects captured in the model were grade 3/4 AEs, and QoL associated with each activity. Patient benefits experienced on AAP compared with BSC (PP) with respect to pain and fatigue were indirectly captured as part of the on-

treatment utility gain. Time spent receiving anti-cancer treatment is another critical model activity as it involves drug acquisition and administration costs.

PFS is an important endpoint in oncology trials, as time to progression has been shown to be a predictor of OS [82;83] and because the progression-free period while on an oncology treatment may be associated with different HRQL and costs than the progressed period. It is therefore important to differentiate between progression-free and progressed health in oncology models and to capture potential benefits of being progression free for a longer period of time. Time to treatment discontinuation collected in the COU-AA-302 trial was considered to be a proxy for PFS due to evidence (both criteria for discontinuation and reasons for discontinuation) that discontinuation is closely associated with progression (see Table 17 in section 6.3.8). Specifically, 74% of the patients who discontinued treatment in the AAP arm and 77% of patients who discontinued treatment in the BSC (PP) arm did so due to disease progression. This concept is consistent with the clinical perception that AA is a medicine that is used on a treat-to-progression basis.

Time spent receiving active anti-cancer treatment is another critical model component. Not only does active treatment duration define drug and administration costs for each treatment arm, but incremental differences in on-treatment follow-up costs, medical resource utilisation (MRU), AEs, and utility also drive both cost and effectiveness and serve to differentiate comparators.

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

Table 34: Key features of the analysis

Factor	Chosen values	Justification
Time horizon	Lifetime	The time horizon in the base case is lifetime to capture the full benefits of treatment. The median OS in the COU-AA-302 trial was approximately 35 months for AAP [18]. Further, a time horizon of 10 years or longer has been used in previous economic assessments in prostate cancer [101] and other advanced cancers [150]. All patients enter the model when treatment begins and exit the model at death or once the maximum age of 100 years is reached, whichever comes first. The model has the capability to examine shorter time horizons of 5 and 10 years
Cycle length	N/A	A discrete event simulation does not use model cycles
Half-cycle correction	N/A	A discrete event simulation does not use model cycles so half cycle corrections are not relevant
Were health effects measured in QALYs; if not, what was used?	Yes, LYG and QALYs	OS is the ultimate outcome in late-stage oncology trials. As a result, LYG by patients receiving one treatment compared to another is a critical measurement. In addition, we consider the possibility that HRQL is different at different phases of disease and with different treatment regimens. To measure this impact, time spent in each treatment phase was adjusted by QoL/utility, spent in that phase to determine ‘quality-adjusted’ life

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 as per the NICE methods guide [15]
Perspective (NHS/PSS)	NHS	The model takes the perspective of the NHS in England and Wales. A societal perspective was also considered; however, due to the disease severity and older nature of the patient population, productivity loss is negligible. Hence, a societal perspective was not relevant and indirect costs were not included in the evaluation

AAP, abiraterone acetate plus prednisolone; HRQL, health-related quality of life; LYG, life years gained; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PSS, personal social services; QALYs, quality-adjusted life years; QoL, quality of life.

Technology

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

Yes.

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

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

Patients on AAP should discontinue treatment at signs of disease progression. In COU-AA-302, patients could take study treatment until radiographic disease progression and/or unequivocal clinical progression, although treatment could be continued in case of radiographic progression but no unequivocal clinical progression [4]).

7.3 Clinical parameters and variables

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

Clinical data
A simple DES approach was used to track patients and their experiences at the individual level. Statistical analyses were performed using data from study COU-AA-302 [18] to inform time to key events in the model (discontinuation, death) and to reflect the current (previously described) treatment pathway in the UK.

For any given treatment phase, the model used data from the COU-AA-302 study to predict the length of time a patient would spend on treatment, whether they discontinued due to an AE, or whether they may have died based on their individual characteristics (age, fitness, treatment history). The model also used these data to predict when each of these events would occur; the event with the shortest predicted time was the one the model assumed to occur. A new series of possibilities and probabilities were then recalculated. For example, if, for a given patient, the time to the end of docetaxel treatment is 4 months and the predicted time to death is 12 months; the patient would finish their docetaxel treatment and subsequently die 8 months later. If the patient's predicted time to death was 2 months, they would die prior to finishing their treatment with docetaxel. All of the prediction equations were based on data from the pivotal COU-AA-302 study and could be varied according to different patient characteristics. For further information, please see section 7.2.4.

Prediction equations
Patient-level data from the COU-AA-302 trial (third planned interim data cut with 55% of death events [18]) were used to inform time spent in each period of the treatment pathway described in the model structure section. A series of statistical equations were developed from the COU-AA-302 trial to predict patient performance status (ECOG, PSA progression, radiographic progression, opiate use) over time as well as time to specific events (treatment start, treatment end, death) dependent on patient characteristics and treatment experience.

The time to treatment start/discontinuation prediction equations included:
- Time from AAP/BSC (PP) treatment discontinuation to docetaxel start
- Time from docetaxel start to docetaxel discontinuation
- Time from docetaxel discontinuation to post-docetaxel treatment start
- Time from third-line treatment start to post-docetaxel treatment discontinuation.

Survival prediction equations included:
- Time from AAP/BSC (PP) discontinuation to death before docetaxel start
- Time from docetaxel start to death before docetaxel discontinuation
- Time from docetaxel discontinuation to death before third-line treatment starts
- Time from post-docetaxel treatment discontinuation to death.

Patient disease status prediction equations included:
- ECOG status over time (at treatment discontinuation and at the start of new treatment)
- PSA progression at discontinuation of AAP/BSC (PP)

- Radiographic progression at discontinuation of AAP/BSC (PP)
- Opiate use at discontinuation of AAP/BSC (PP).

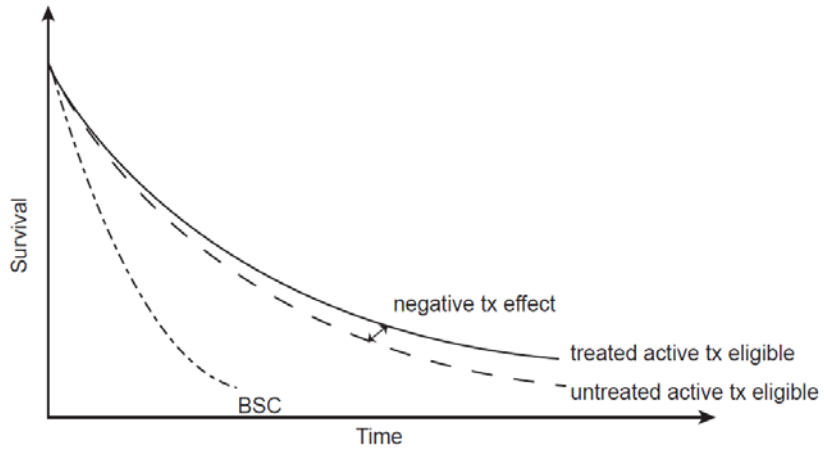
These equations were estimated by exploring different parametric fits for Kaplan–Meier data from the COU-AA-302 trial, including Weibull, lognormal, log-logistic, exponential, and gamma and selecting a model based on the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) and visual inspection. AIC and BIC are used to measure how well the data are described by alternative models and the distribution giving the smallest criterion value was selected as the best-fitting model (refer to appendix 16 for details on model selection). When Weibull was not found to be the best fit, it is added as an alternative function in the model when predicting treatment duration (time to AAP/BSC [PP] end), as the log-logistic function has a long tail and may lead to extreme values for treatment duration. The statistical analyses were performed following the NICE Decision Support Unit guidelines [151] and are described in detail in appendix 16.

The final prediction equations used in the base model to estimate the duration of time until the next event or death occurs are shown in Table 143 to Table 151 in appendix 16. These tables provide the distribution of the event and survival times (exponential, Weibull, log-logistic, or log-normal), describe the parameters that influence each event time, and provide the parameter estimates. Table 152 in Appendix 16 also gives the prediction equations used to update disease characteristics (ECOG, PSA progression, radiographic progression, and opiate use) at different time points in the simulation model. Change in ECOG is estimated using a cumulative logit model, while a binary logit model is used to predict PSA progression, radiographic progression, and opiate use. Additional details on the prediction equations (functional fit statistics, p values) are provided in appendix 16.

Post-docetaxel active treatment effect

Because cabazitaxel is not recommended by NICE, patients who were otherwise eligible in the AAP arm did not receive active treatment after docetaxel, even though they might have received cabazitaxel in the COU-AA-302 trial (refer to section 7.2.2). It was also assumed that these patients would not receive re-treatment with AAP. As cabazitaxel use can prolong both PFS and OS compared to BSC (PP), the results would have been biased if the clinical benefits associated with cabazitaxel were not adjusted for in the data utilised in the model. Therefore, patients in the AAP arm who **did not** receive post-docetaxel active treatment in the model followed the same survival observed in the COU-AA-302 trial. A 'negative' treatment effect to account for cabazitaxel use in the COU-AA-302 study was applied to the group eligible for active treatment in this phase (for time to post-docetaxel active treatment discontinuation, time from post-docetaxel treatment end to death) based on data from the COU-AA-301 trial data (Figure 13).

Figure 13: Estimating untreated post-docetaxel treatment-eligible patients' survival



BSC, best supportive care; tx, treatment.

More specifically, time to treatment discontinuation and time from treatment discontinuation to death were analysed using COU-AA-301 trial data, using AAP treatment as a predictor (versus PP). The coefficients of AAP of the two equations (0.5174 for time to treatment discontinuation and –0.1493 for time from treatment discontinuation to death) were inversely included in the survival prediction equations described in Table 145 to Table 151 in appendix 16. Time from post-docetaxel start to post-docetaxel end and time from third-line treatment end to death are shown in Table 35.

Table 35: Adjusting the untreated post-docetaxel treatment-eligible patients' survival

	Time from post-docetaxel start to end	**Time from third-line treatment end to death**
Intercept	5.2241	7.1534
Negative treatment effect	–0.5174	0.1493
Adjusted intercept	**4.2981**	**7.3027**
Scale	0.8717	0.8123

AAP is accepted for post-docetaxel treatment, so this was allowed as an option in the BSC arm. Enzalutamide is now also available for the treatment of mCRPC in the post-docetaxel setting and NICE has recently issued new draft guidance recommending enzalutamide as an option for treating mCRPC if their disease has progressed during or after one docetaxel regimen. As AAP and enzalutamide have demonstrated a survival benefit in this post-docetaxel phase, the modelling approach accommodated the survival curves observed with each subsequent treatment option using data from the COU-AA-302 trial. The use of enzalutamide as a post-docetaxel treatment option was tested in a scenarioanalysis.

Incidence of grade 3/4 AEs

AEs affect both costs associated with taking a given drug, as well as the HRQL of patients receiving treatment. Since the safety profile of a given drug can be a differentiating factor in cost-utility analyses (CUAs), the impact of AEs was considered in the model. Grade 3 or 4 AEs related to the treatment but not to the disease of mCRPC itself were included in the model analysis. AEs that occurred at varying rates per treatment were prioritised (14 were identified), as incremental

differences between treatments are the specific focus of pharmacoeconomic analyses and drive results. As the pre-docetaxel treatments have a relatively tolerable safety profile, the AEs selected were driven by the docetaxel AE profile.

For the two pre-docetaxel treatments, AAP and BSC (PP), the cost impacts of AEs were captured implicitly in the analyses of event-related MRU (section 7.5.6). On the whole, data from the COU-AA-302 trial indicated that the AE rates were similar between arms. Grade 3 or 4 TEAEs occurred in 49.3% of AAP patients and 43.5% of patients in PP patients [18]. Similarly, the cost impact of AEs for the post-docetaxel treatment, AAP (post-docetaxel) and BSC (PP post-docetaxel) were captured implicitly in the analyses of event-related MRU based on the COU-AA-301 trial data (section 7.5.6). Therefore, in the pre- and post-docetaxel phases, no incremental AE effects were considered.

For docetaxel treatment, because this treatment phase was not directly measured in the COU-AA-301 or COU-AA-302 trials and the model assumed that the baseline event-related MRU of docetaxel is the same as AAP (post-docetaxel), the incremental grade 3 or 4 AE rates for docetaxel vs. AAP (post-docetaxel) were considered for cost implications. Table 36 lists the difference between the grade 3/4 docetaxel [47;152] and AAP (post-docetaxel) [85] AE rates considered in the model in relation to costs. Note that the event rates were not adjusted for potential differences across the trials and trial populations.

Table 36: Incremental frequency of grade 3/4 AEs with docetaxel vs. AAP (%) [47;85;152]

	Docetaxel vs. AAP (%)
Neuropathy[a]	4.0
Neutropaenia	31.9
Febrile neutropaenia[a]	3.0
Thrombocytopaenia	–0.4
Anaemia	–2.8
Oedema	–2.5
Hypokalaemia	–4.4
Hypertension	–1.3
Arthralgia	–4.1
Asthenia/fatigue	–7.4
Diarrhoea	0.9
Dyspnoea	1.2
Nausea	0.9
Vomiting	–0.7

[a]AEs that are relevant for the subsequent therapies only.

Summary

Data from multiple sources were used to inform the model as summarised in Table 37. The COU-AA-302 trial was the primary data source used to assign individual patient profiles, generate prediction equations, and estimate AEs and costs. Additional key sources included published literature (AEs, utilities) and the British National Formulary (BNF) and NHS (costs).

Table 37: Summary of key model data sources

Parameter	**Data source**
Patient profiles	COU-AA-302 trial [65]
Prediction equations	COU-AA-302 trial, third planned interim data cut with 55% of death events

	captured [18]
AEs	Published literature (docetaxel) [47;152] and AAP (post-docetaxel) [85]
Utilities	Oxford Outcomes UK utility study [153], published literature [154], COU-AA-302 trial mapping study [155]
Costs	UK list price and BNF (drug acquisition), NHS reference costs (drug administration) [156], COU-AA-302 trial (unplanned MRU), UK cost file (AEs and terminal cost), KOL survey for scheduled follow-up cost

AAP, abiraterone acetate plus prednisolone; AE, adverse event; BNF, British National Formulary; BSC, best supportive care; KOL, key opinion leader; MRU, medical resource use; NHS, National Health Service, PP, placebo plus prednisolone.

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

A Markov model was not used in this analysis; therefore, an estimation of transition probabilities is not applicable. Instead, a time-to-event individual simulation approach was employed. Section 7.2.4 explains how times progresses in the simulation model.

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

N/A; please refer to section 7.3.2.

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

Intermediate outcome measures were linked to the primary clinical outcome measure from the COU-AA-302 trial. OS is the most relevant outcome measurement in late stage oncology trials, and OS is the co-primary endpoint for the COU-AA-302 Phase III trial. A series of prediction equations were used to estimate times to specific events (treatment start, treatment discontinuation, death) which ultimately project patients' OS. These prediction equations relate individual patient attributes/surrogate markers to a time to treatment start/discontinuation and death distribution from which a specific time can be drawn.

Patient disease status was updated based on the COU-AA-302 data at the start and discontinuation of treatment including ECOG PS value, and whether the patient experienced PSA progression, radiographic progression, and/or opiate use. The following equations were derived to update disease status, and disease status variables served as predictors in the time-to-event prediction equations (i.e. impact OS):

- ECOG PS over time (at treatment discontinuation and at the start of new treatment)
- PSA progression at discontinuation of AAP/BSC (PP)
- Radiographic progression at discontinuation of AAP/BSC (PP)
- Opiate use at discontinuation of AAP/BSC (PP).

Change in ECOG PS was estimated using a cumulative logit model, while a binary logit model was used to predict PSA progression, radiographic progression, and opiate use. Refer to appendix 16 for a detailed explanation of how the cumulative logit and binary logit models are implemented in the simulation.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

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

Clinical components were not based on expert recommendations. Rather, COU-AA-302 Phase III trial data was used to formulate prediction equations (see section 7.3.1). The effectiveness of AAP was estimated based on a series of survival functions: time to AAP/BSC (PP) treatment discontinuation, time to docetaxel start, time from docetaxel start to end, time to post-docetaxel active treatment, and time to death before, during, and after docetaxel. These equations ultimately estimate patients' OS and time spent with each treatment.

Summary of selected values

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

[3] 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 38: Summary of variables applied in the economic model

Parameter	Value / Source	SE (distribution) / Alternative	Reference to section in submission
Model settings			
Population at baseline	COU-AA-302 trial profiles [65]	N/A	7.2.6
Time horizon (years)	Lifetime	5 years, 10 years	7.2.6
Discount rate for costs, %	3.5	User modifiable	7.2.6
Discount rate for health, %	3.5	User modifiable	7.2.6
Prediction equations	COU-AA-302 trial, third interim analysis [18]	N/A	7.3.1
Clinical: Effectiveness	Prediction equations		7.3, appendix 16
Time to AAP/BSC (PP) discontinuation	Log-logistic[a] model	Weibull model	
Time from AAP/BSC (PP) treatment discontinuation to docetaxel	Log-normal model	N/A	
Time from docetaxel start to docetaxel discontinuation	Weibull model	N/A	
Time from docetaxel discontinuation to post-docetaxel treatment start	Weibull model	N/A	
Time from third-line treatment start to post-docetaxel treatment discontinuation	Weibull model	N/A	
Time from AAP discontinuation to death before docetaxel start	Weibull model	N/A	
Time from BSC (PP) discontinuation to death before docetaxel start	Weibull model	N/A	
Time from docetaxel start to death before docetaxel discontinuation	Log-logistic model	N/A	
Time from docetaxel discontinuation to death before third-line treatment starts	Weibull model	N/A	
Time from post-docetaxel treatment discontinuation to death	Weibull model	N/A	
Clinical: Intermediate predictors	Prediction equations		7.3, appendix 16
ECOG PS over time (at treatment discontinuation and at the start of new treatment)	N/A	N/A	
PSA progression at discontinuation of AAP/BSC (PP)	N/A	N/A	
Radiographic progression at discontinuation of AAP/BSC (PP)	N/A	N/A	
Opiate use at discontinuation of AAP/BSC (PP)	N/A	N/A	
Clinical: AE rates	Published literature (docetaxel) [47;152] and AAP (post-docetaxel) [85]	N/A	
Costs, £			
Comparator drug costs	UK PAS price; BNF online (accessed December 2013)		7.5.5
AA per 30-day supply	[redacted]		
BSC (prednisolone per 30-day supply)	2.59		
Docetaxel per 3-week cycle	1,069.50		

Drug administration cost	[156]; SB12Z		7.5.5
AA	0.00		
BSC (PP)	0.00		
Docetaxel per 3-week cycle	214.00	21.40	
Chemotherapy related G-CSF costs			7.5.5
G-CSF cost per administration cycle (3 weeks)	686.38	68.64	
Scheduled, disease-related follow-up costs (monthly), median (IQR)			7.5.6
Pre-docetaxel on-treatment cost			
AAP	217.22	129.24; 266.77	
BSC (PP)	82.40	43.56; 158.26	
Docetaxel			
BSC (pre-docetaxel)	82.40	43.56; 158.26	
Docetaxel	203.46	107.22; 248.79	
Post-docetaxel active treatment			
BSC (post-docetaxel)	116.01	47.69; 159.14	
BSC (PP post-docetaxel)	116.01	47.69; 159.14	
AAP (post-docetaxel)	198.76	96.76; 223.37	
BSC (before death)	39.86	21.54; 124.59	
Unplanned MRU (monthly)			7.5.6
Pre-docetaxel on-treatment cost			
AAP	93.79	Lognormal distribution	
BSC (PP)	93.79		
Docetaxel			
BSC (before docetaxel)	93.79		
Docetaxel	380.29		
Post-docetaxel active treatment			
BSC (post-docetaxel)	380.29		
BSC (PP post-docetaxel)	380.29		
AAP (post-docetaxel)	380.29		
BSC (before death)	380.29		
AE costs			7.5.7
Neuropathy	561.38		
Neutropaenia	808.50		
Febrile neutropaenia	5,147.50		
Thrombocytopaenia	703.80		
Anaemia	1,178.80		
Oedema	899.93		
Hypokalaemia	1,214.25		
Hypertension	474.33		
Arthralgia	212.26		
Asthenia	29.67		
Diarrhoea	1,363.51		
Dyspnoea	0.00		
Nausea	695.13		
Vomiting	2,042.78		
End of life			7.5.8
Terminal cost (one-off)	3,598.00	359.80	
Utilities			
Post-ADT baseline	[redacted]	[redacted]	
AAP on-treatment utility increment	[redacted]	[redacted]	
BSC (pre-docetaxel)	[redacted]	[redacted]	
Docetaxel	[redacted]	[redacted]	
Post-docetaxel	[redacted]	[redacted]	
BSC (before death)	0.500	0.080	

[a]Alternate survival functions are used to describe time to AAP/BSC (PP) discontinuation represented by a log-logistic distribution. Log-logistic models have long tails (resulting in extreme estimates for

time on treatment), and cost-effectiveness is influenced by mean time on treatment, which is strongly influenced by the tail of the survival curve. To improve face validity of extrapolations, a different survival model (Weibull) for the long flat segment of the survival curve could be applied.
AAP, abiraterone acetate plus prednisolone; ADT, androgen-deprivation therapy; AE, adverse event; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony stimulating factor; MRU, medical resource use; N/A, not applicable; PP, placebo plus prednisolone; PSA, prostate-specific antigen; SE, standard error.

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

Costs and clinical outcomes were extrapolated beyond the trial follow-up. OS is the most relevant outcome measurement in late-stage oncology trials, and OS is the co-primary endpoint for the COU-AA-302 Phase III trial. The amount of time to follow patients during the trial was limited and we aimed to capture survival outcomes beyond the trial time horizon, thus following all patients until death. In the third interim data analysis of the trial data, in which 55% of death events were reached, the median OS was 35.3 months for the AAP arm and 30.1 months for the PP arm. In order to project OS for the entire model time horizon, approaches for extrapolating survival data beyond the trial period were required.

A series of prediction equations were used to estimate time to specific events (treatment start, treatment discontinuation, death) which ultimately project patients' OS. Prediction equations include:

- Time to AAP/BSC (PP) treatment discontinuation
- Time to docetaxel start
- Time from docetaxel start to end
- Time to post-docetaxel active treatment
- Time to death before, during, and after docetaxel.

Time on and between treatment is an important measurement in economic models. Not only does active treatment duration define drug and administration costs for each comparator, but incremental differences in on-treatment follow-up costs, MRU, AEs, and utilities drive both cost and effectiveness and serve to differentiate comparators.

The economic model assigned times to treatment start, treatment discontinuation, and death for each patient at each line of treatment based on the prior treatments received and other characteristics. This was accomplished with statistical equations that relate individual patient attributes to a time to treatment start/discontinuation and death distribution from which a specific time can be drawn. Parametric survival analysis techniques were used to identify an appropriate distribution (exponential, Weibull, log-normal, or log-logistic) that captures the shape of the hazard of event, and incorporate predictors that can increase or decrease the hazards. Detailed steps on how the parametric survival analysis was conducted are provided in appendix 16.

The performance of four models (using the exponential, Weibull, log-normal, and log-logistic distribution) for estimating time-to-event outcomes were tested. The AIC and BIC measures, used to assess how well the data are described by alternative models, were used to identify the best fitting distribution (see appendix 16 for model selection details). The final prediction equations used in the base model to estimate the duration of time until the next event or death occurs are shown in Table 143 to Table 151 (appendix 16). Additional details (functional fit statistics, p values) on each prediction equation are presented in appendix 16.

Next, the observed clinical trial data (i.e. Kaplan–Meier survival curves) for OS in the AAP and BSC (PP) treatment arms were compared against predicted OS estimates from the simulation model. Comparison of the observed and simulated OS curves is shown in section 7.8.

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

Table 39: Key assumptions for clinical inputs

Assumption	Justification
Extrapolation beyond trial period is based on data observed in the COU-AA-302 trial, and censored patients followed the trend/pattern of those who had events	Follows Decision Support Unit survival analysis technical report [151]
The model assumes that all patients survive beyond the end of 1st-line AAP or BSC (PP) treatment	In the COU-AA-302 trial (55% of events data cut [18]), only 5 patients died while on treatment with AAP or BSC (PP) (3 and 2 patients, respectively); rather death occurs after treatment stop. Thus, prediction equations were developed to predict time to death from the time of AAP or BSC (PP) treatment stop (refer to appendix 16 for a detailed explanation)
Patients whose ECOG PS is ≥2 at the end of AAP/BSC (PP) are not eligible for docetaxel treatment and these patients use BSC until death	NICE recommends docetaxel for men with mCRPC only if Karnofsky PS ≥60% [147], which is approximately ECOG PS <2. Also, clinical experts in the UK (interview with Murray Yule and John Frew Sept/Oct 2012) indicated that docetaxel should not be given to individuals whose ECOG PS is ≥2
The untreated post-docetaxel active treatment-eligible patients follow the same survival observed in the COU-AA-302 trial but with a 'negative' treatment effect based on data from the COU-AA-301 trial	As cabazitaxel prolongs both PFS and OS compared to BSC (PP), the results would be biased if we did not adjust the clinical benefits associated with cabazitaxel as observed in the COU-AA-302 trial
As cabazitaxel is not approved by NICE in the UK, AAP-arm patients are assumed to receive BSC (before death) only after docetaxel treatment failure, and the BSC (PP)-arm patients receive AAP after docetaxel if they are eligible for it	Post-docetaxel active treatments (e.g. cabazitaxel) reflect observations/predictions from the COU-AA-302 trial. To reflect the UK setting, patients who were eligible to receive the post-docetaxel treatments as observed in the COU-AA-302 trial were not actively treated after docetaxel failure but rather with BSC only
Although every possible treatment pathway that might occur is not captured in the model, we assume that the majority of pathways are modelled based on the COU-AA-302 trial data	COU-AA-302 trial data; the percentages of pathways captured in the AAP and BSC (PP) arms are 93% and 91%, respectively (see appendix 16 for the treatment pathway distribution in the COU-AA-302 trial AAP and BSC [PP] arms)

AAP, abiraterone acetate plus placebo; BSC, best supportive care; KOL, key opinion leader; OS, overall survival; PFS, progression-free survival; PP, placebo plus prednisolone.

7.4 Measurement and valuation of health effects

Patient experience

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

The clinical burden of prostate cancer varies depending on whether the disease is locally advanced or metastatic. Localised disease can exist for many years without symptoms, and is associated with good survival rates due to the fact that the majority of prostate tumours are slow growing [157]. Recent statistics show that the 5-year US survival rate is effectively 100% when the disease is local or regional [42].

Metastatic disease, however, is associated with significant clinical symptoms, and increased mortality [157]. In the US, the 5-year survival rate drops to 31% for disease with distant metastases [42]. Patients with mCRPC can present with asymptomatic or symptomatic disease. Asymptomatic or mildly symptomatic prostate cancer is defined by a BPI-SF #3 score of 0–1 (asymptomatic) or 2–3 (mildly symptomatic) and a score of 0–1 on the ECOG PS instrument. When a patient does become symptomatic, the main symptoms include: weight loss and loss of appetite, lower extremity pain, oedema due to obstruction of venous and lymphatic tributaries by nodal metastases, uraemia due to obstruction of the urethra, and SREs. Uraemic symptoms can also occur from urethral obstruction caused by local prostate growth or retroperitoneal adenopathy secondary to nodal metastasis [23;157]. SREs due to bone metastases are major contributors to morbidity, inducing bone pain, skeletal remodelling, fractures, and anaemia [158].

CRPC can arise at different stages of disease progression; however, it typically arises at, or rapidly leads to, the metastatic disease stage. Once the cancer has become castration resistant, average survival is poor. An examination of mCRPC trials found a median OS of 20.9 months (95% CI 18.5–22.8 months) for patients responding to first line chemotherapy treatment, and 11.1 months (95% CI 8.8–12.6 months) for those who did not respond [159]. In addition to the symptoms and morbidities associated with late-stage prostate cancer described above, patients with mCRPC have typically undergone extensive treatment, which may contribute to considerable further clinical burden. Key treatment-related clinical problems that may affect mCRPC patients include [160]: pelvic pain after prostatectomy, urinary dysfunction (particularly after prostatectomy and radiation therapy), bowel dysfunction after radiation therapy, erectile dysfunction, infertility after prostatectomy, increased infections, tiredness, hair loss, sore mouth, loss of appetite, nausea, and vomiting as a result of chemotherapy.

In addition to clinical symptoms, prostate cancer, as with other cancers, is associated with a substantial psychological burden on patients due to the severity of the disease and fear associated with it [26]. The most common psychological symptoms expressed by men with prostate cancer are anxiety and depression, which often co-exist. A recent study on the psychological burden of prostate cancer found that 38% of men with prostate cancer reported scores at or above the cut-off for psychological distress (a combined score of 15 or above using the Hospital Anxiety and Depression Score instrument) [25]. A further study has reported that approximately 6% of men suffering from prostate cancer report signs of high distress

and probable psychological co-morbidity. Disease stage was found to be a significant predictor for poorer mental health [26]. The most common single diagnosis in this group was post-traumatic stress disorder [26].

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

QoL 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. Studies demonstrate that the HRQL of patients with mCRPC declines considerably in the last months before death [161], and the scores from patients with metastatic disease are lower in terms of functioning, physical and social domains, compared to patients with localised disease [162]. Patients with mCRPC suffer from disease symptoms and can also be impacted by the side effects of treatments. Symptoms such as nausea, vomiting, dyspnoea, appetite loss, and pain have been observed to worsen with time [154;161]. Of all the factors affecting HRQL, however, pain is usually considered the most prominent factor for patients at this stage of their disease [163]. Pain control is therefore considered to be paramount to improve symptom burden and thus HRQL in mCRPC patients [164]. As a further decline in HRQL of mCRPC patients is associated with progression, delaying this will have substantial benefits to patient HRQL. 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 HRQL. 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 [165].

HRQL data derived from clinical trials

7.4.3 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 COU-AA-302

The HRQL of patients in COU-AA-302 was measured using the FACT-P (FACT – general and prostate cancer subscale) questionnaire on the first day of cycles 1, 3, 5, and 7, and then on the first day of every third cycle and at treatment discontinuation [4;66]. Whilst the FACT-P offers a well-validated and clinically meaningful assessment of disease burden [66], it does not offer preference-adjusted health status (utility) values that are essential to pharmacoeconomic models. In

contrast, the EuroQoL five dimensions (EQ-5D) assessment is a standardised and validated generic instrument that establishes these preference-adjusted utility values [166;167]. Although algorithms have been developed to map FACT-P to EQ-5D [61], the approach taken for the model was to gather UK-specific EQ-5D data over a broader range of the treatment phases than captured in the COU-AA-302 study.

UK mCRPC patient utility study

The study aimed to collect health utility values for mCRPC stratified by treatment phases, suitable for inclusion in the cost-effectiveness decision analytic model that may include various treatments at different stages of the patient journey. The study also aimed to collect HRQL data to develop understanding of the different experiences of men with mCRPC, in particular patients who are asymptomatic or mildly symptomatic and have not yet received chemotherapy.

The study was non-comparative and consequently did not allow for direct comparisons of the utility impact of AAP with that of BSC. Accordingly, the study assumed that patients experience the same utility regardless of the treatment administered, provided that they are in the same treatment phase.

Patients with mCRPC were classified into one of the following four subgroups reflecting treatment phases:

1. Mildly or asymptomatic after failure of ADT; chemotherapy not yet clinically indicated
2. Symptomatic after failure of ADT; chemotherapy clinically indicated but not started
3. After failure of ADT; receiving chemotherapy
4. After failure of ADT; post-chemotherapy.

Treatment phases used for classification of participants in the study were first and foremost guided by the model treatment phases, but they were also guided by what was feasible and relevant in a cross-sectional study. For example, an active monitoring stage is perhaps a treatment phase more feasible to capture in a longitudinal study than in a cross-sectional study. In this study, patients who were screened to define the symptomatic phase before chemotherapy might include both patients who receive only BSC (i.e. never go on to receive chemotherapy), as well as some that might go on to receive docetaxel (BSC pre-docetaxel as per our model definition).

Utility and HRQL data, along with background and medical history data, were collected via an online survey among participants recruited through a specialist patient recruitment agency and patient advocacy groups. The sample consisted of 163 UK men with mCRPC who had previously taken anti-androgen tablets for >1 month but had since stopped (unless they had undergone orchiectomy/orchidectomy).

Further details about this study can be found in appendix 17.

Results

Data were collected from a total sample of 163 men with mCRPC, representing:

- asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy (N=50)

- symptomatic post-ADT, pre-chemotherapy (N=50)
- receiving chemotherapy at the time of participation (N=17)
- completed one or more round of chemotherapy (N=46)

Participants in each of these four groups had a mean age of 72±9, 70±12, 60±15, and 68±9 years, respectively. Most men (94–100%, depending on group) were white.

Utility values
EORTC 8D and EQ-5D-5L utility values for the four mCRPC stratified treatment phases are shown in Table 40. Out of the four treatment phases, both measures estimate the **highest** mean utility for men who are **asymptomatic/mildly** symptomatic and have not yet received chemotherapy and the **lowest** mean utility for men who are **symptomatic** but have not yet received chemotherapy. Mean utilities estimated for chemotherapy and post-chemotherapy indicate relatively similar utility decrement for these two treatment phases which fall between the first two treatment phases (asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy and symptomatic post-ADT, pre-chemotherapy). Participants' global ratings of their own health (EQ-5D visual analogue scale [VAS]) show a similar pattern of HRQL impact across the four mCRPC treatment phases (Table 40).

Table 40: Utilities by treatment phase

Measure	**mCRPC treatment phase**			
	Asymptomatic/ mildly symptomatic post-ADT, pre-chemotherapy (N=50)	**Symptomatic post-ADT, pre-chemotherapy (N=50)**	**Currently receiving chemotherapy (N=17)**	**Post-chemotherapy (N=46)**
EORTC 8D utility				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L utility				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

[a]This value was felt to be too high, and was reduced to 0.5. Reasons for this are detailed below
CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation; VAS, visual analogue scale.

The recruited sample allowed utility values to be elicited from subgroups of close to 50 cases for three of the mCRPC treatment phases. Fewer men with mCRPC participated in the study who were receiving chemotherapy treatment at the time of survey completion, resulting in utility values for the third mCRPC treatment phase being elicited from a relatively small sample (N=17).

The data showed a similar pattern of mean utilities/HRQL impact across mCRPC

treatment phases. The asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy participants had higher utility/better HRQL than the symptomatic before chemotherapy participants. Mean utilities/HRQL for men with mCRPC post-ADT, pre-chemotherapy showed a similar pattern for asymptomatic versus mildly symptomatic and physically able (ECOG 0) versus those able to carry out light work but not strenuous activities (ECOG 1).

Mean utility values for men receiving chemotherapy were similar to those post-chemotherapy. However this was a relatively small group and participants in the third mCRPC treatment phase were much younger than those in the other treatment phases. Given the size of this group, one should be relatively cautious when interpreting their QoL status and in making generalisations to other mCRPC patients receiving chemotherapy.

Capturing data from people receiving chemotherapy is challenging, and it is possible that the small number who participated in this study may represent relatively younger and healthier patients. This might result in a mean utility value that is higher than might be expected. Accordingly, sensitivity analyses around utility estimates were conducted. Substituting alternative utility values in sensitivity analyses indicated that utility values were not a primary driver of model results which were relatively stable under different utility scenarios (sections 7.6.1).

There was a high correlation between the utility values elicited by the EQ-5D-5L (generic) and EORTC 8D (cancer-specific) measures. However, mean EORTC 8D utilities for all four mCRPC treatment phases were higher than those elicited by the EQ-5D-5L. This is consistent with a previous comparison of scores elicited by these two instruments in multiple myeloma [168]. Rowen et al. [168] concluded that EQ-5D values tend to be lower than EORTC-8D; and the EORTC-8D showed greater sensitivity to change in milder health states. Differences in utility values elicited by the two instruments are likely explained by the relatively narrower range in utilities that can be calculated from the EORTC 8D preference-weighted algorithm, the fact that as a generic instrument the EQ-5D may be more likely to capture the additional HRQL impact of any comorbidities, and the fact that current scoring of the EQ-5D-5L maps to preference-weights developed from UK valuation of the previous EQ-5D-3L [169]. The UK EQ-5D-3L value set [170] offers a notably wide range in potential utilities, particularly for more severe states. Development of new value sets for the EQ-5D-5L is currently underway [171], with the existing EQ-5D-3L UK value set and mapped EQ-5D-5L currently accepted for HTA submissions.

Given NICE's preference for using EQ-5D utility values, these values were used in the base-case economic analysis in preference to the EORTC 8D mapped utility values.

Utility values estimated for subgroups of mCRPC treatment phases (asymptomatic/mildly symptomatic mCRPC patients before receiving chemotherapy) are shown in Table 41 and summarised below:

- Asymptomatic patients (BPI 0–1) reported higher utility than mildly symptomatic patients (BPI 2–3). This was reflected by both EORTC 8D and EQ-5D-5L values. The 95% CIs around the mean values overlapped between the BPI subgroups, although this was only a marginal overlap for values elicited by the EQ-5D-5L

- Patients self-reporting the equivalent of ECOG classification 0 (not physically limited in any way) reported significantly higher utility than those self-reporting the equivalent of ECOG classification 1 (able to walk and carry out light work but unable to do more strenuous activities). This difference was seen with both EORTC 8D and EQ-5D-5L instruments, with no overlap in 95% CIs between the ECOG classification disease state 1 subgroups.

Table 41: Utilities by symptoms, age, and ECOG PS subgroups

Measure	Asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy			
	BPI #3		ECOG PS	
	0–1 (N=31)	2–3 (N=19)	0 (N=23)	1 (N=26)
EORTC 8D utility				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L utility				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L VAS				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

BPI, Brief Pain Inventory; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; VAS, visual analogue scale.

Mean EORTC QLQ-C30 and PR-25 domain scores are reported in Table 175 and Table 176 (appendix 17). The pattern of impact reflected by the EORTC QLQ-C30 global health status is similar to that shown by the utility data, with highest scores reported by men in the first treatment phase (asymptomatic/mildly symptomatic before receiving chemotherapy), lowest scores from the second treatment phase (symptomatic before receiving chemotherapy) (Table 175). Global health status of men in the third and fourth treatment phases (currently receiving chemotherapy and post-chemotherapy) were quite similar and fell between those of the first and second treatment phases.

Compared with men in the second, third, and fourth mCRPC treatment phases, asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy (first mCRPC treatment phase) reported notably less functional HRQL impact on Physical functioning, Role functioning, and Social functioning (Table 175). They also reported relatively less impact on Emotional functioning and marginally less impact on Cognitive functioning. Role functioning and Social functioning were particular areas of HRQL for symptomatic patients who had not received chemotherapy (second mCRPC treatment phase). Social functioning was also particularly impacted for those receiving chemotherapy (third mCRPC treatment phase). In terms of symptoms, scores were lower amongst the first treatment phase participants across the range captured by the EORTC QLQ-C30 compared with the second, third and fourth treatment phases. Patients in the second treatment phase scored highest for fatigue, pain, dyspnoea, and appetite loss. Patients in the third treatment phase scored highest for nausea and vomiting, diarrhoea, and financial difficulties.

In terms of prostate cancer-specific HRQL, wide SDs and small sample sizes make it hard to draw conclusions about any differences between respective treatment phases in terms of sexual activity and sexual functioning (Table 176). However, asymptomatic/mildly symptomatic post-ADT, pre-chemotherapy patients (first mCRPC treatment phase) reported less urinary symptoms than those in the other mCRPC treatment phases and less bowel symptoms than symptomatic post-ADT, pre-chemotherapy patients and those receiving chemotherapy (second and third mCRPC treatment phases). Mean scores for incontinence aid were lower in chemotherapy naïve patients (first and second subgroups) than those receiving/post-chemotherapy (third and fourth subgroups), although wide SDs around the mean values for the first and second mCRPC treatment phases indicate considerable variation in experience.

Other utility values

Since AAP was not available as a NICE-recommended treatment option in the post-ADT setting at the time of the utility study, it was assumed these patients were treated with BSC. A utility increment of [redacted] (derived from the COU-AA-302 trial data) was applied to those patients who received AAP post-ADT. This on-treatment utility increment was calculated utilising the mapping study referenced in appendix 18.

The post-docetaxel utility increment of 0.046 (derived from COU-AA-301 trial data) was not applied since the majority of patients were assumed to already have been receiving AAP in this setting. Hence, it was assumed this utility gain was captured in the UK mCRPC Utility Study and to apply it would have been double-counting. These assumptions were explored in sensitivity analyses.

In order to be consistent with the Janssen STA submission for AA (Zytiga®) for the treatment of mCRPC following previous cytotoxic therapy [61], a utility value of 0.50 was assumed for patients in the BSC group before death. A study by Sandblom et al. was used to estimate this utility value by calculating the average observed over the last 8 months of life [154]. Utilities from this study ranged from 0.58 (patients with 8–12 months of remaining survival) to 0.46 (patients with <4 months survival remaining) (see section 4.4.5). Given that mCRPC patients are likely to spend their last 6–8 months of life in the progressed health state, the average utility of 0.50 was used with a standard error of 0.08. Additional sensitivity analyses have been conducted around these estimates. Table 42 provides a summary of all the utility values associated with each treatment phase of the model.

Table 42: Summary of the utility values associated with each model phase

Utilities	Value	SE (distribution)	Source
Post-ADT baseline	[redacted]	[redacted]	UK mCRPC patient utility study
AAP on-treatment utility increment	[redacted]	[redacted]	COU-AA-302 mapping study
BSC (pre-docetaxel)	[redacted]	[redacted]	UK mCRPC patient utility study
Docetaxel	[redacted]	[redacted]	UK mCRPC patient utility study
Post-docetaxel	[redacted]	[redacted]	UK mCRPC patient utility study
BSC (before death)	0.500	0.08	Sandblom et al. [154]

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- **Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.**
- **Details of the methodology used.**
- **Details of validation of the mapping technique.**

To examine the impact of different utility values on the overall results, utility values generated using a mapping analysis were used in a sensitivity analysis (please refer to section 7.4.3). In the COU-AA-302 study, QoL was measured using FACT-P questionnaire. A review of the literature for the AAP post-chemotherapy NICE submission [61] identified a mapping study by Wu et al. [172], but there was an error in the algorithm within this publication. Therefore a study was undertaken to produce an algorithm for mapping FACT-P to EQ-5D.

Prediction model

A prediction model for mapping FACT-P to EQ-5D was constructed and validated in 602 patients with mCRPC in six European countries (including the UK) [155]. Utility values were derived from EQ-5D profiles based on a UK-specific EQ-5D value set. Patients who were pre-chemotherapy (▇▇▇▇), during chemotherapy (▇▇▇▇), or post-chemotherapy (▇▇▇▇); and none had received AAP. All patients completed FACT-P and EQ-5D instruments, and the mapped FACT-P results were compared with the actual EQ-5D results. Predictive validity of the five FACT-P subscales, patient demographics, co-morbidities, and prior chemotherapy for utility values was tested using ordinary least squares (OLS), median, Gamma and Tobit multivariate regression models. Ten-fold cross validation techniques were employed to derive goodness of fit statistics. Predictive ability of the algorithms was assessed by comparing observed and predicted EQ-5D scores for three patient subgroups (pre-, during, post-chemotherapy). OLS-regression was the best-performing model, and explained approximately ▇▇▇▇ of the observed EQ-5D variation (R2, based on a 10-fold cross-validation). All FACT-P subscales were significantly predictive; and the OLS algorithm was found to have good predictive ability, with a high degree of correlation between observed and predictive EQ-5D scores. Further details can be found in appendix 18.

FACT-P to EQ-5D Mapping Study

In the COU-AA-302 study, QoL was measured using the FACT-P questionnaire on day 1 of cycles 1, 3, 5, 7, 10, etc.; at treatment discontinuation; and at study end. FACT-P scores were mapped onto EQ-5D utilities using an OLS regression algorithm. The results of this are shown in Table 43. These values were used in the some of the scenario analyses for the economic model (see sections 7.6.1 and 7.7.9).

Table 43: Results of the FACT-P to EQ-5D Mapping Study

State	Base case (all patients)	
	Utility value	SE
Post-ADT baseline (asymptomatic and mildly symptomatic)	[redacted]	[redacted]
AAP on-treatment utility increment	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Docetaxel utility decrement	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]
BSC (PP post-docetaxel)	[redacted]	[redacted]
AAP (post-docetaxel)	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]

AAP, abiraterone acetate plus prednisolone; AE, adverse event; BPI, brief pain inventory; BSC, best supportive care; SE, standard error.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

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

- HRQL information for the comparator relevant to the decision problem
- Utility/disutility values for the health states associated with mCRPC.

These research questions were explored by updating the systematic review undertaken by NICE for the docetaxel HTA review published in 2006 (TA101) [147], which was subsequently updated for the NICE STA submission for AA to address the treatment of mCRPC following previous cytotoxic therapy [61].

Published literature databases were searched from 01.01.05 (the year of the TA101 search [147] was conducted) to 02.09.13. The literature databases searched are listed in Table 44.

Table 44: Literature databases searched

Database
MEDLINE® (including MEDLINE® In-process, and other non-indexed citations)
Excerpta Medical Database (Embase®)
Cochrane® (including Cochrane systematic reviews, other reviews, clinical trials, economic evaluations, NHS EED)
EconLit®

EED, Economic Evaluation Database; NHS, National Health Service.

The search strategies used in the TA101 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 44. The translated searches were validated by confirming that they returned the seven studies identified and included in the HRQL review of the TA101 assessment. The translated search strategies are presented in appendix 12. Please note that the EconLit® database was searched via

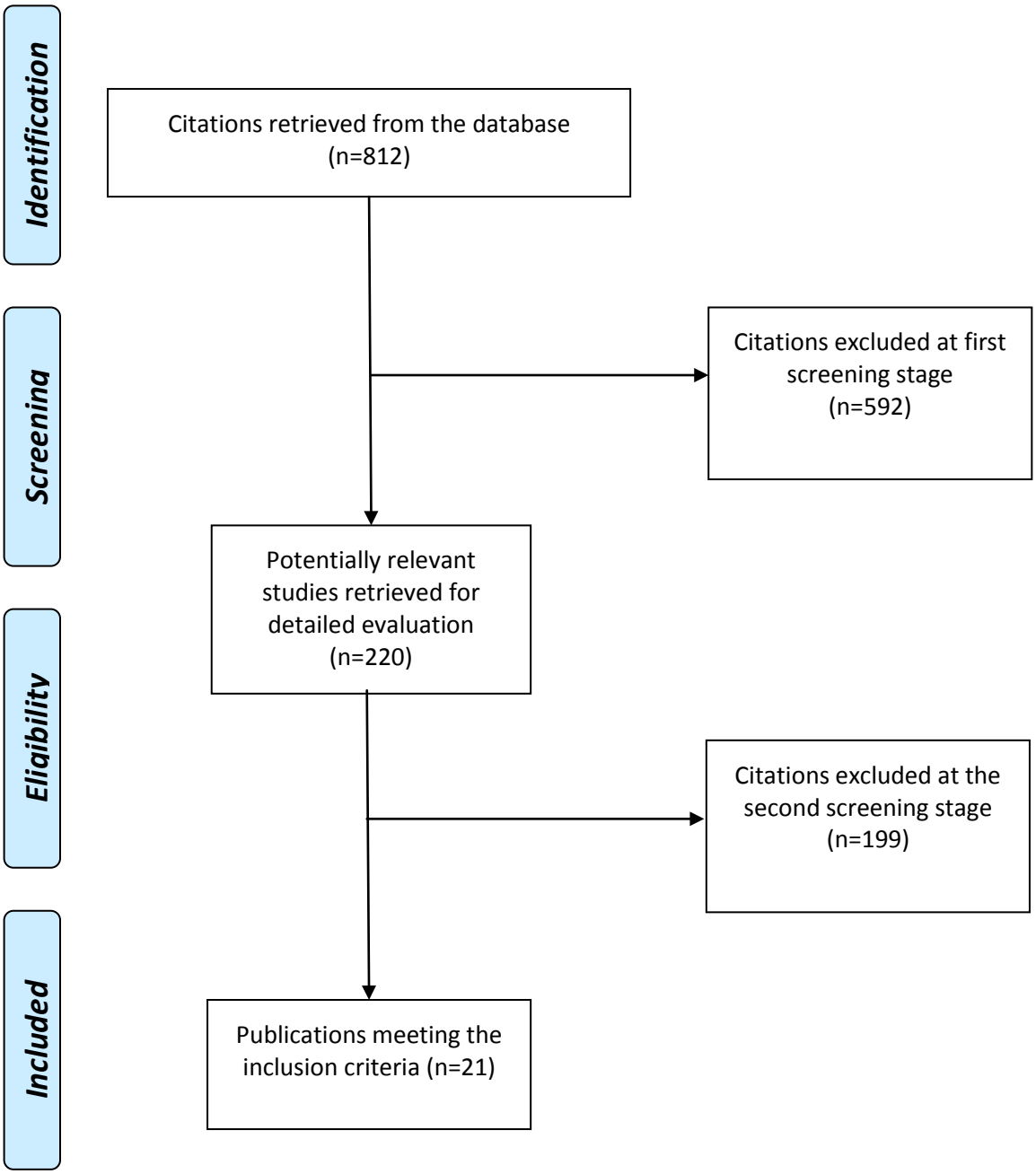
the AEAweb.org platform in a previous review of HRQL in patients with advanced metastatic prostate cancer, with no studies meeting the inclusion criteria identified. This search method was also used for retrieval of HRQL information in support of the previous NICE STA submission for abiraterone acetate to address the treatment of mCRPC following previous cytotoxic therapy [61].

To be included in the review, studies had to meet pre-defined eligibility criteria, which were specified in the protocol (see appendix 12). In brief, studies were excluded if they were not primary studies or were not in a population (or contained a subgroup) of patients with advanced or metastatic disease. To be included, studies needed to report utilities or HRQL-specific measures.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded and imported into 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 meet 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. In instances where it was not possible to include or exclude citations based on the title and abstract, full-text copies were ordered. The pre-defined 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 812 citations; screening of these citations based on the information provided in their titles and abstracts excluded 592 citations (any copies and duplicates were also excluded at this stage). Full texts were obtained for the remaining 220 citations and they were screened based on the information provided in their full texts. The literature review identified 21 studies that assessed HRQL in a mCRPC patient population. A summary of the systematic review flow is given in Figure 14.

Figure 14: Trial flow diagram for the systematic review of relevant HRQL data



A summary of the measures reported in each of the 21 studies included in the present review update are captured in Table 45.

Table 45: Summary of QoL measures captured in 21 studies identified in the updated systematic review of relevant HRQL data

	EQ-5D	SF-36	HUI	PORPUS	QLQ-C30	FACT-P/ FACT-G	BSI	Other
[173]		X					X	Mini-MAC
[174]	X							
[175]		X						
[176]					X	X		
[177]						X		
[155]	X					X		
[178]		X						UCLA PCI-SF, McCorkle and Young's Symptom Distress Scale, FACIT-Sp, PEPPI
[179]	X					X		
[180]	X							
[181]		X						UCLA-PCI
[182]	X		X	X	X			PCI
[183]		X						BSI, DAS, FRI, CIDI
[184]		X						
[185]	X					X		
[186]								Utility data derived from standard gamble and time trade off
[161]	X				X	X		
[187]	X							15D
[188]		X						10-point VAS
[189]	X					X		
[172]								Utility mapping study: FACT-P to EQ-5D
[190]		X						

15D, the 15 dimensions instrument of health-related quality of life; BSI, brief symptom inventory; CIDI, Composite International Diagnostic Interview; DAS, disease activity score; EQ-5D, EuroQoL Five Dimensions; FACIT-Sp, Functional Assessment of Chronic Illness Therapy Scales Spirituality subscale; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-P: Functional Assessment of Cancer Therapy – Prostate; FRI, Family Relationships Inventory; HUI, Health Utilities Index; Mini MAC, Mini-Mental Adjustment to Cancer scale; PCI, Prostate Cancer Index; PCI-SF, Prostate Cancer Index short form; PEPPI, Perceived Efficacy in Patient–Physician Interactions; PORPUS, Patient Oriented Prostate Utility Scale; SF-36, Short Form 36; UCLA, University of California in Los Angeles; VAS, visual analogue scale.

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

- **Population in which health effects were measured.**
- **Information on recruitment.**
- **Interventions and comparators.**
- **Sample size.**
- **Response rates.**
- **Description of health states.**
- **Adverse events.**
- **Appropriateness of health states given condition and treatment pathway.**
- **Method of elicitation.**

- **Method of valuation.**
- **Mapping.**
- **Uncertainty around values.**
- **Consistency with reference case.**
- **Appropriateness for cost-effectiveness analysis.**
- **Results with confidence intervals.**
- **Appropriateness of the study for cost-effectiveness analysis.**

A NICE HRQL systematic review published in 2007 identified eight studies that provided utility values [101]. An update of this review identified 21 HRQL studies, of which eight provided utility values of potential use in the model [155;161;174;179;180;185;187;189]. Information on these studies was available from conference abstracts only, with very few study details reported. A summary of utility values identified in the literature (from the original NICE review and the update) is presented in Table 46.

Table 46: Spectrum of HRQL utility values for prostate cancer, updated from the NICE HTA review conducted as part of TA101 [191]

Source	---------- SPECTRUM OF DISEASE SEVERITY ---------->									Methodology
	Localised			Metastatic			mCRPC			
[174]							0.698			EQ-5D (mean, baseline N=100)
[192]			0.92		0.83				0.42	TTO (Median), physician's opinion (N=47)
			0.88		0.53				0.05	Patients with localised prostate cancer, patient's opinion (N=27)
			0.78		0.58				0.05	Patients with metastatic prostate cancer, patient's opinion (N=17)
[193]		0.78			0.51				0.2	TTO (mean), Impersonal (N=31)
		0.78			0.72				0.35	TTO (mean), Personal (N=28)
[194]		0.84			0.66				0.23	TTO (mean), Patient opinion (N=57)
[155]							0.67			Utility derived from EQ-5D profiles based on a UK-specific EQ-5D value set (N=699)
[179]	0.77			0.59						EQ-5D (mean), Value (N=201)
[180]							0.63			EQ-5D (mean), Value (N=74)
[195]		0.86				0.85				Patient PORPUS–U(SG) Mean (N=141)
		0.8				0.75				Patient PORPUS–U(RS) Mean (N=141)
		0.8				0.81				HUI Mean
		0.66				0.62				QWB Mean
[154]			>16 m				16–8 m	8–4 m	4–0 m	months before death (>16 m patients still alive at time of analysis)
			0.77				0.58	0.54	0.46	EQ-5D (mean), Value
			70				57	53	45	EQ-5D (mean), VAS
[185]							0.59	0.76		EQ-5D (mean), Value (N<291)
[186]	0.84	0.81	0.71	0.67					0.25	SG (mean), Patients (N=162)
[161]							0.635			EQ-5D (mean baseline) Total patients (N=280)
							0.715			EQ-5D (mean baseline) UK patients (N=29)
[187]	0.90	0.89	0.87	0.74						EQ-5D (Mean, N=630)
	0.91	0.89	0.88	0.80						15D (Mean, N=630)

[196]					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)
[189]							0.72			EQ-5D (mean), Value (N=101)

15D, the 15 dimensions instrument of health-related quality of life; EQ-5D, EuroQoL Five Dimensions; HRQL, health-related quality of life; HTA, health technology assessment; HUI, Health Utilities Index; m, months before death; mCRPC, metastatic castration-resistant prostate cancer; NICE, National Institute for Health and Clinical Excellence; PORPUS-U(SG), Patient Oriented Prostate Utility Scale, standard gamble; PORPUS-U(RS), Patient Oriented Prostate Utility Scale, rating scale; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

Of the eight HRQL studies identified in the HTA 259 update [154;161;186;192-196], the study by Sandblom et al. [154] was deemed most appropriate to use in the HTA 259 appraisal [154]. This study examined HRQL in 1,442 prostate cancer patients who were approaching death and therefore provided a good estimate of utility for the post-progression state in the model. It was felt that this study provided a better estimate of utility in the end stages of life than the patient utility study discussed in section 7.4.3. Full details on the use of this utility can be found in the Other utility values part of section 7.4.3.

The study by Sandblom et al. and the eight studies identified in the present review update that provide utility values of potential use in the model are briefly summarised in Table 47, in order to explore their relevance to the present economic evaluation.

Table 47: Summary of studies that provide utility values of potential use in the model

Study	Country/countries of study	Study objective	Patient population	Study methodology	Relevant utilities data reported	Appropriateness to the current decision problem
Bahl 2013 [174]	UK	To report UK final QoL and updated safety data from a single-arm EAP following the TROPIC clinical trial	Patients with mCRPC previously treated with a docetaxel-containing regimen receiving cabazitaxel 25 mg/m^2 IV every 3 weeks with oral prednisolone 10 mg daily (N=108)	A single-arm EAP in 12 centres following the TROPIC clinical trial (Phase III)	Mean (range): Baseline (N=100) 0.698 (0.654–0.741) Cycle 2 (N=97) 0.730 (0.689–0.770) Cycle 4 (N=74) 0.765 (0.719–0.812) Cycle 6 (N=63) 0.761 (0.716–0.805) Cycle 8 (N=37) 0.781 (0.711–0.851) Cycle 10 (N=28) 0.817 (0.743–0.891) Post-treatment (N=62) 0.695 (0.633–0.756)	No data are reported that are specific to chemotherapy-naive patients with asymptomatic or mildly symptomatic mCRPC. Data presented for patients on cabazitaxel
Diels 2012 [155]	Belgium, France, Germany, Sweden, Netherlands, UK	To construct and validate a prediction model of preference-adjusted health status (EQ-5D) for mCRPC patients using FACT-P	Patients with confirmed mCRPC and documented disease progression (N=699), with a mean age of 72.1 years, a mean time since diagnosis of 6.6 years, and a mean time since ADT failure of 4.1 years, of which 32% of patients were treated with chemotherapy, 24% had prior chemotherapy, and 43% were chemotherapy-naive	An observational study conducted in 47 centres that collected HRQL data	The mean EQ-5D utility measured was 0.67 for the whole population examined	Subgroup data were not reported for only patients in the UK or for only patients who were chemotherapy-naive

Hechmati 2012 [179]	France, Germany, Italy, Spain, UK	To evaluate the impact of bone metastases on utility (using EQ-5D) and quality of life (using FACT-P) in high-risk CRPC patients	Patients with CRPC at high risk for developing bone metastases (N=3,477)	Data were extracted from the Adelphi Real World Prostate Cancer Disease-Specific Programme©, a cross-sectional survey of 348 urologists and oncologists and their prostate cancer patients, which was conducted between December 2009 and May 2010	Patients with CRPC and a high risk of developing bone metastases had a mean EQ-5D index score of 0.59 (N=36) while patients with CRPC and bone metastases already had a mean EQ-5D index score of 0.59 (N=165)	Subgroup data were not reported for only patients in the UK or for only patients who were chemotherapy-naive
James 2011 [180]	France, Germany, UK, US	To describe correlates of utility assessments in patients with mCRPC who had progressed during or after docetaxel first-line therapy	Patients with mCRPC who have progressed during or after docetaxel first-line therapy (N=74), the median age was 72 years for the subset of patients who had an evaluable EQ-5D questionnaire	A multicentre observational study	The mean (SD) utility index score was 0.63 (0.26) for the 74 patients who had an evaluable EQ-5D questionnaire	No UK-specific data were reported. Patients were not chemotherapy-naive
Spencer 2012 [185]	France, Germany, Italy, Spain, UK	To construct and validate a prediction model of preference-adjusted health status (EQ-5D) for mCRPC patients using FACT-P	Patients with mCRPC (N=291), with a mean age of 70.7 years. A total of 57% of patients were treated with chemotherapy at the time of assessment, 10% had prior chemotherapy, and 33% were chemotherapy-naive	Patient-level data were obtained for CRPC patients from the Adelphi Group Prostate Cancer Disease Specific Program. Country specific utility values were derived from EQ-5D profiles based on value sets available for 8 countries and the EU	Mean estimated country-specific utilities varied between 0.59 (New Zealand) and 0.76 (Germany)	No UK-specific data, or data specific to chemotherapy-naive patients, were reported

Sandblom 2004 [154]	Sweden	To determine how HRQL is affected by approaching death in men with prostate cancer	All men with prostate cancer in the county of Östergötland, Sweden	A questionnaire including the EuroQol (EQ-5D 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 1,442 men with prostate cancer	The EQ-5D score for men who died of prostate cancer was 0.538 (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).	No data are reported that are specific to chemotherapy-naive patients with asymptomatic or mildly symptomatic mCRPC relevant to the UK population
Sullivan 2007 [161]	Australia, Canada, France, Germany, Italy, UK, US	To report on the longitudinal HRQL findings of a multinational, multicentre, observational study of patients with diagnosed mCRPC	Patients with mCRPC; mean age 72 years; 98% Caucasian	An observational, multicentre, multi-national cohort study (N=280) designed to explore HRQL (EORTC QLQ-C30, FACT-P and EQ-5D) in an mCRPC population	Baseline EQ-5D scores were 0.635 (total population) and 0.715 (UK)	No data specific to a chemotherapy-naive population were reported
Torvinen 2013 [187]	Finland	To compare the HRQL of prostate cancer patients with that of the general population; to compare the results obtained by different HRQL instruments; to explore factors associated with the resultant HRQL scores	Patients >18 years old diagnosed with prostate cancer were eligible for the study (N=630)	Cross-sectional observational survey. 630 prostate cancer patients (local disease, metastatic, palliative care) assessed their HRQL with the generic 15D and EQ-5D, as well as the cancer-specific EORTC QLQ-C30 questionnaires	Mean±SD (95% CI) for the metastatic group: • EQ-5D (N=85): 0.74±0.27 (0.69–0.80) • 15D (N=88): 0.80±0.12 (0.78–0.83) • VAS (N=86): 66.79±21.80 (62.12–71.46)	No UK-specific data were reported. Subgroup data were not reported for mCRPC or for only patients who were chemotherapy-naïve

Wolff 2012 [189]	Germany	To assess HRQL outcomes in mCRPC patients	Patients with confirmed prostate cancer diagnosis and mCRPC (N=101); mean age 73.2 years. At inclusion, 32.6% had never been treated with chemotherapy, 36.8% had been treated with chemotherapy previously and 30.5% were currently undergoing chemotherapy	A 1-year, observational, cross-sectional, prospective study conducted in 37 German prostate cancer specialised centres	The mean (SD) EQ-5D single index utility scores were 0.72 (0.30) for the whole population, 0.81 (0.27) for patients who were chemotherapy-naive, 0.66 (0.30) for patients who had been treated with chemotherapy previously, and 0.64 (0.31) in patients undergoing chemotherapy. The mean (SD) EQ-5D VAS score was 47.8 (23.6) for the whole population	No UK specific data were reported

15D, the 15 dimensions instrument of health-related quality of life; ADT, androgen deprivation therapy; CI, confidence interval; CRPC, castration-resistant prostate cancer; EAP, early access programme; EORTC QLQ, Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQoL Five Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HRQL, health-related quality of life; IV, intravenously; mCRPC, metastatic castration-resistant prostate cancer; SD, standard deviation.

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

Only one utility value was taken from the literature search: 0.5 for BSC (before death), which was based on a study by Sandblom et al. [154], as it was felt that this more accurately captured the end stage of the disease and this was also the value used in the application for AAP post-chemotherapy (section 7.4.3).

The utility values mapped from the COU-AA-302 study (section 7.4.4) were only used in one of the scenario analyses (scenario 4; sections 7.6.1 and 7.7.9). Data from the study were also used to calculate the utility increment for AAP over BSC (PP).

The majority of the model used utility values from the UK mCRPC utility study (section 7.4.3) that was carried out specifically for this submission.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

AEs associated with treatment of mCRPC are common. AEs associated with abiraterone acetate are generally manageable, and infrequently resulted in dose reductions, dose interruptions or discontinuations [197].

A review of the literature identified several studies in metastatic cancers that indicate the impact of commonly occurring AEs (Table 48). In those studies reporting utilities for grade 3, grade 4, or severe AEs, the values ranged from 0.05 to 0.261.

Table 48: Disutility of AEs from the published literature

Source	**[198]**	**[199]**	**[200]**	**[201]**	**[202]**	**[203]**	**[204]**	**[205]**
Elicitation Method/Tool	EQ-5D	SG	SG	TTO	EQ-5D	SG	VAS and SG	TTO
Disease Area	NSCLC	MBC	CLL	Chemotherapy-related anaemia	NSCLC	NSCLC	NSCLC	MRCC
AE grade	Unknown	3/4	Unknown	Mild, moderate, severe	Unknown	'Severe'	Unknown	3
Diarrhoea	0.126	0.103	–	–	–	–	0.0468	0.261
Nausea	0.136		–	–	–	–	0.04802	0.255
Vomiting	–	0.103	–	–	–	–	0.04802	–
Neutropaenia	0.127	–	–	–	–	–	0.08973	–
Febrile neutropaenia	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	–	–

AE, adverse event; CLL, chronic lymphocytic leukaemia; EQ-5D, EuroQoL Five Dimensions; MBC, metastatic breast cancer; MRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

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

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

The patient utility study was non-comparative and consequently did not allow for direct comparisons of the utility impact of AAP with that of BSC. Accordingly, the study assumed that patients experience the same utility regardless of the treatment administered, provided that they are in the same treatment phase. To account for this in the model, an on-treatment utility increment of [redacted] was applied to the baseline utility for AAP (see section 7.4.3 for further details).

Table 49: Summary of quality-of-life values for cost-effectiveness analysis

Treatment phase	Model treatment phase	EQ-5D	Justification
Asymptomatic /mildly symptomatic post-ADT	Post-ADT baseline AAP or BSC (PP)	[redacted]	The mCRPC utility study captured the baseline utility value for those patients who are asymptomatic/mildly symptomatic having failed ADT.Since AAP has a safety profile similar to PP in the 302 trial, application of additional AE utility decrement over BSC (PP) was not necessary.
AAP on-treatment utility increment	Post-ADT baseline AAP	[redacted]	The survey did not ask the participants about their current mCRPC treatment. Utility increment assumed to capture AAP on-treatment effect
Symptomatic post-ADT	BSC (pre-docetaxel)	[redacted]	Utility reflected the impact of treatment and AEs.
Currently receiving chemotherapy	Docetaxel	[redacted]	Utility reflected the impact of treatment and AEs
Post-chemotherapy	BSC (post-docetaxel); AAP (post-docetaxel); BSC (PP post-docetaxel)	[redacted]	The survey did not ask the participants about their current treatment post-docetaxel. Since AAP is reimbursed in the post-docetaxel setting, this utility value can be viewed as the average utility of patients receiving BSC post-docetaxel, AAP (post-docetaxel), BSC (PP post-docetaxel). Therefore, it may not be necessary to apply utility increment for AAP (post-docetaxel). Because AAP has a safety profile similar to PP in the 301 trial, application of additional AE utility decrement was not necessary
Post-chemotherapy	BSC (before death)	0.5	Utility value derived from published literature reflected further disease progression before death [154]

AAP, abiraterone acetate plus prednisolone; AE, adverse event; BSC, best supportive care; mCRPC, metastatic castration-resistant prostate cancer; PP, placebo plus prednisolone.

Summary for the application of utility impact of treatment and AEs:

- Because AAP has a safety profile similar to PP in both the COU-AA-301 and COU-AA-302 trials, indicating few treatment-related AEs, the application of additional AE utility decrement is not necessary
- There is a need to explicitly consider the utility increment from treatment for pre-docetaxel AAP
- There is no need to consider the utility increment from treatment with AAP in the post-docetaxel setting as it is assumed that this is captured in the UK mCRPC Utility Study.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

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

N/A.

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

The model was not structured around a set of health states, but instead patients experienced events that define the model structure. The simulation estimated the time spent in an activity (i.e. time between events) such as time on treatment or BSC using the prediction equations (explained in section 7.3). Utilities/QALYs are associated with time spent in each activity (on active treatment or BSC) in the simulation model. As per NICE guidelines, all QALYs were discounted at an annual rate of 3.5%. The continuous discounting function (Equation 2) below was used to compute the present value (PV) of a utility U to be received T days (time an activity is terminated) from the time an activity is initiated (T_0), assuming a rate r of 3.5%, continuously discounted. (A similar formula applies for discounting costs over time where the health state utility value U is replaced by the cost linked to the activity). Discounted QALYs were estimated at the termination of each activity over the time

[4] 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.

spent in the activity, and total QALYs for patients from the start of AAP/BSC (PP) treatment were summed over time.

– ———— (Equation 2)

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

While studies exist in peer-reviewed literature that present the utility of prostate cancer based on a variety of preference elicitation techniques, QoL endpoints were measured within the mCRPC utility study (section 7.4.3), and this was deemed the most appropriate source for these data given that no other literature-based study population matched that of the AAP trial.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

As the model is an individual time-to-event simulation model, there were no explicit health states. Individual patients were assigned a baseline utility value of [redacted] for the ITT population; [redacted] for the BPI #3 0–1 subgroup; and [redacted] for the ECOG PS subgroup.

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

HRQL was not assumed to remain constant over time. During each activity (e.g. time on active treatment or BSC) estimated by the prediction equations in the simulation model, patients occupied a particular health utility value. This value accounted for the current activity (e.g. on active treatment or BSC) and impact of AEs on the HRQL of patients receiving treatment. The utility value was weighted by the amount of time spent in each activity.

AEs affect both costs associated with taking a given drug, as well as the HRQL of patients receiving treatment.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Utility values from sections 7.4.3 to 7.4.8 have not been altered from the estimates calculated in the mCRPC utility study (section 7.4.3) analysis.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The only tariff relevant to the clinical management of mCRPC patients is for those patients who become symptomatic and consequently receive docetaxel.

NHS reference 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.

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

Whilst AA is not a chemotherapy, and therefore not associated with a chemotherapy tariff, this tariff is relevant to those patients who become symptomatic and receive chemotherapy as a result. Cost sources used in the model include:

- Drug costs for the interventions and concomitant medications were collected from the BNF (accessed online 12.13)
- Unit costs for chemotherapy administration, as well as clinical scheduled follow-up procedures were determined using the UK National Schedule of Reference Costs 2012–2013 [156]
- Unit costs for Outpatient visits and Community Nurse visits were determined from the Unit Costs of Health and Social Care (2012) [206].

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- **country of study**
- **date of study**
- **applicability to UK clinical practice**
- **cost valuations used in study**
- **costs for use in economic analysis**
- **technology costs.**

The systematic review previously described in section 7.1 encompassed economic evaluations and studies of the burden and costs of advanced and metastatic prostate cancer. The review identified 40 potentially relevant publications [207-246]. However, only four of these included costs from a UK setting [224;233;236;240]. It should be noted that three of these studies [224;233;240] were identified in the systematic search of relevant resource data for the UK conducted for the earlier NICE STA 259 submission for AAP for the treatment of mCRPC following previous cytotoxic therapy [61]. The four UK studies are summarised in Table 50.

Table 50: Studies of the burden and costs of advanced and metastatic prostate cancer identified in the systematic review that included costs from a UK setting

Study	Country/countries of study	Study objective	Patient population	Study methodology	Relevant cost/resource utilisation reported	Applicability to clinical practice in England and Wales and the current decision problem
Dass 2012 [236]	Belgium, France, Germany, Sweden, Netherlands, UK	To assess healthcare resource utilisation in mCRPC patients during treatment	Patients with mCRPC, mean age 73.0 years (N=212)	1-year retrospective observational study conducted in 47 centres specialised in prostate cancer	Rates of utilisation of prostate cancer-related surgery, palliative radiotherapy, hospitalisation, and emergency room use for the population stratified by whether patients were chemotherapy-naive, undergoing chemotherapy, or had chemotherapy in the past	The study didn't capture healthcare resource use by treatment which was required for the economic model.It was therefore more appropriate to use the mCRPC resource use survey.
Hechmati 2011[233]	Germany, Italy, Spain, UK	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)	Patients with bone metastases secondary to breast, prostate, or lung cancer (N=478)	A multicentre, prospective, observational study. Healthcare utilisation data were collected retrospectively by chart review for all SREs occurring in the 90-day period before study enrolment, and prospectively for the duration of the patients' participation in the study	Mean length of stay for all skeletal-related events and individual SREs in the UK were reported, but not specific to prostate cancer	Resource utilisation specifically attributable to prostate cancer not reported

Oosterhof 2003 [247]	Belgium, Denmark, Netherlands, UK	To compare toxicity, subjective response rates, time to subjective progression and OS in patients with painful bone metastases of HRPC treated with strontium-89 or palliative local field radiotherapy with the usual radiotherapy regimen	Patients with painful bone metastases of HRPC (N=101)	Phase III RCT	Costs associated with strontium-89 or palliative local field radiotherapy with the usual radiotherapy regimen	Resource utilisation data were not reported separately for UK patients versus other countries; approximately 25% of patients received chemotherapy during the study
Oglesby 2008 [240]	UK	To characterise the hospital burden associated with metastatic bone disease and SREs following breast and prostate cancer	Patients with metastatic bone disease and SREs following breast and prostate cancer (N=28,130)	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	This study explored admission and re-admission rates across these two cancer types, and the average length of stay for prostate cancer patients with metastatic bone disease and SREs was 43 days. The mean cost of admission was higher for prostate cancer patients with metastatic bone disease and SREs compared to other reasons for admission (£3,618 vs. £1,871)	Resource use data specific to patients in the UK with prostate cancer were reported

HRPC, hormone-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; RCT, randomised controlled trial; SRE, skeletal-related event.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

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

Scheduled MRU

The 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 UK standard practice in treating an average mCRPC patient, a survey was designed to obtain the scheduled MRU values associated with the different phases of mCRPC. The generation of these data involved online quantitative market research with 53 oncologists and 50 urologists from Medeconnect (part of Doctors.Net; a panel of doctors who have agreed to participate in market research surveys) [248]. Participants underwent 30–40-minute self-administered online interviews. Participants had to be a member of the Royal College of Physicians and/or the Royal College of Radiologists; be a Consultant, Associate Specialist, Staff Grade/Specialty Doctor, or Specialty Trainee/Registrar Years 4+; and make treatment decisions for mCRPC patients.

After completing several screening questions, a series of survey questions were asked to determine estimates of MRU associated with scheduled follow-up over a 3-month period. Clinicians were asked to complete the survey with reference to patients who occupied pre-docetaxel, during docetaxel, post-docetaxel, BSC, and palliative care stages of the mCRPC disease pathway. Each question asked for the percentage of patients requiring that particular resource and if relevant, the number of resource units used per patient. Questions covered total outpatient visits, scans (CT, MRI, bone, ultrasound, electrocardiogram [ECG]) and laboratory tests (full blood count [FBC], liver function, renal function, PSA, and ‘other’). The MRU data collected were subsequently used to calculate MRU costs associated with scheduled follow-up for different health states in the simulation model. The SPC states that patients receiving AA require additional monitoring for the first 3 months of treatment, therefore higher MRU in AAP patients in both the pre- and post-docetaxel setting

[5] 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.

was applied in the model for the first 3 months of starting AAP treatment. Thereafter patients were assumed to receive the same level of MRU of the respective BSC, be it pre- or post-docetaxel. The base-case analysis utilised only the values reported by oncologists, as in clinical practice in the UK, a large proportion of mCRPC patients are treated by oncologists. The values obtained from urologists were used in scenario analysis.

Unscheduled MRU

The COU-AA-301 and COU-AA-302 trials recorded resources consumed as a result of unplanned events while on treatment, such as AEs. Statistical analysis of these data was conducted to assess how unscheduled MRU (and therefore costs) differed between treatment arms.

Due to the absence of data specific to BSC (pre-docetaxel), docetaxel and BSC (post-docetaxel), assumptions had to be made for the unplanned event-related cost. Since patients on BSC (pre-docetaxel) are most similar to those on BSC (PP) they were assumed to have the same unplanned event-related MRU as BSC (PP) treated patients from the study. For docetaxel, it is assumed that baseline resource utilisation was equivalent to the placebo arm of the COU-AA-301 trial and any incremental cost difference was caused by grade 3/4 AEs (a detailed explanation is provided in section 7.5.7). BSC (post-docetaxel) was also assumed to have a similar unplanned event-related MRU as the placebo arm of the COU-AA-301 trial.

Since, in the model, patients switch to BSC (before death) strategies when they were close to death, it was assumed that patients would incur a similar level of unplanned event-related cost at this stage of disease regardless of their prior treatment history. Because the MRU data were not collected for this disease stage and patients in the COU-AA-301 trial had advanced disease and fairly short life expectancy, the MRU cost from the COU-AA-301 trial was used in the model for BSC as a best proxy.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The dosing of the active treatment options matched those in section 1.10, those used in Phase III clinical trials, and those in the SPCs (Table 51). For docetaxel, in which dosing is determined based on body surface area, a body surface area of 2.08 m^2 was used, calculated [249] from the average weight and height observed in the COU-AA-302 trial. The model allows the user to select whether to consider wastage for docetaxel and considered drug wastage in the base case.

Table 51: Dosing regimens implemented in the economic model

	Dose per administration	Dose frequency	Administration	Doses per month
AA	1,000 mg	Daily	Oral	30.4
BSC (PP)	10 mg	Daily	Oral	30.4
Docetaxel	75 mg/m^2	Every 3 weeks	IV	1.4

AA, abiraterone acetate; BSC, best supportive care; IV, intravenous; PP, placebo plus prednisolone.

The cost for AA was assumed to be £2,930 per 30 days. Janssen has previously agreed to supply AA with a PAS involving a confidential discount. Under the terms of the PAS, the cost of AA used in the model is £[redacted] per month ([redacted] discount). This PAS is in place for all current and future indications under consideration by NICE and is therefore used in the base-case analysis. A scenario analysis demonstrating the cost-effectiveness of AA without the PAS is also provided as commercial in confidence. As reported in the COU-AA-302 trial, a compliance rate of 98% for AAP patients was considered in the model. Prednisolone cost was used in the model to represent BSC (PP) for costing purposes. The cost of prednisolone is £2.60 per 30-day supply. The cost for docetaxel is £1,069.50 per 160-mg vial, which can be used for one administration for an average mCRPC patient in this model.

Table 52 presents the cost of all the active treatment options. The cost of IV administration was £214 (Code: SB12Z – Chemotherapy Administration, deliver simple parenteral chemotherapy at first attendance), as listed in the 2012–2013 National Schedule of Reference Costs published by the NHS Trust Administration [156]). No administration costs are required for oral drugs. All treatments other than prednisolone monotherapy were assumed to be administered with concurrent prednisolone, 10 mg daily.

Table 52: Unit costs associated with the technology in the economic model

Items	AA cost, £	BSC (PP) cost, £	Docetaxel cost, £	Ref
Cost of technology per month	[redacted]	2.63	1,550.14	BNF online (accessed 12.13)
Administration costs per 3 weeks	0	0	214	[156] (Code SB12Z)
Total cost per month	[redacted]	2.63	1,550.14	

AA, abiraterone acetate; BSC, best supportive care; PP, placebo plus prednisolone.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Scheduled costs

Unit costs for the regularly scheduled follow-up procedures (Table 53) for the survey described in section 7.5.4 were determined using the NHS Reference Costs, 2012–2013 [156].

Table 53: Unit costs associated with scheduled follow-up visits [156]

Resource	Unit cost, £	Code
Out-patient visit (consultant)	127.00	800
CT scan	120.00	RA10Z
Radiographic/MRI scan	198.00	RA03Z
ECG	53.00	DA01
Ultrasound	51.00	RA23Z
Bone scan	192.00	RA36Z
Full blood count	3.64	DAP823
Liver function test	1.25	DAP841
Kidney function test	1.25	DAP841
PSA	1.25	DAP841

CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging; PSA, prostate specific antigen.

The estimated MRU associated with scheduled follow-up over a 3-month period to assess the disease activity and monitor treatment while on a particular treatment regimen is shown in Table 54.

Table 54: Estimated MRU associated with scheduled follow-up by oncologists over a 3-month period to assess the disease activity and monitor treatment while on a particular treatment regimen

	AAP		BSC (PP)		BSC (pre-docetaxel)		Docetaxel		BSC (post-docetaxel)/ BSC (PP post-docetaxel)		AAP (post-docetaxel)		BSC (before death)	
	%	Frequency[a]	%	Frequency[a]	%	Frequency[a]	%	Frequency[a]	%	Frequency[a]	%	Frequency[a]	%	Frequency[a]
Out-patient visit	100	3	85	1	85	1	100	3	90	2	100	3	60	1
CT scan	80	1	30	1	30	1	80	1	30	1	60	1	10	1
Radiographic /MRI scan	20	1	10	1	10	1	5	1	10	1	10	1	5	1
Ultrasound	4	1	0	0	0	0	0	01	0	0	0	0	0	0
Bone scan	50	1	40	1	40	1	50	1	30	1	50	1	10	1
ECG	28	1	0	0	0	0	10	1	0	0	10	1	0	0
FBC	100	3	90	1	90	1	100	3	80	1	100	3	40	1
LFT	100	3	80	1	80	1	100	3	70	1	100	3	20	1
Renal function test	100	3	90	1	90	1	100	3	80	1	100	3	20	1
PSA	100	3	100	1	100	1	100	3	100	1	100	3	50	1

Source: data on file [248].
[a]Per 3 months.
AA, abiraterone acetate; BSC, best supportive care; CT, computed tomography; ECG, electrocardiogram; FBC, full blood count; LFT, liver function test; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

Overall scheduled MRU costs based on the oncologists surveyed are shown in Table 55.

Table 55: Scheduled oncologist MRU costs

	Median, £	25th percentile, £	75th percentile, £
AAP	217.22*	129.24	266.77
BSC (PP)	82.40	43.56	158.26
BSC (pre-docetaxel)	82.40	43.56	158.26
Docetaxel	203.46	107.22	248.79
BSC (post-docetaxel)	116.01	47.69	159.14
BSC (PP post-docetaxel)	116.01	47.69	159.14
AAP (post-docetaxel)	198.76*	96.76	223.37
BSC (before death)	39.96	21.54	124.59

*Cost applied for the first 3 months, and then the equivalent cost of BSC (PP) thereafter (section 7.5.4)
AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Unplanned costs

The resource use for unplanned events while patients were receiving treatment was similar between the AAP and PP arms for the COU-AA-302 trial population. When the treatment was tested as a predictor of unplanned MRU cost, the cost was higher for the AAP arm; however, the difference was not statistically significant (p=0.1298), especially when treatment duration was included in the analysis (p=0.3496). On the contrary, independently, treatment duration was a predictor of unplanned MRU with statistical significance (p=0.0017). In summary, these results indicate that unplanned MRU while on-treatment is associated with treatment duration but not with type of treatment. A similar analysis has been conducted for the COU-AA-301 trial data and found that MRU is independent of treatment arm and treatment duration.

For the COU-AA-302 trial, the main driver of resource utilisation was outpatient visits. Particularly, as patients stayed on treatment longer, more outpatient visits were needed. For the COU-AA-301 trial, the main driver of resource utilisation was hospitalisation and the time-to-first hospitalisation indicated that hospitalisation was probably related to disease progression. While the model has the flexibility to apply the unplanned event-related MRU either as a monthly cost or as a one-off cost, it is applied as a monthly cost in the model base case to be more consistent with the MRU analysis result of the COU-AA-302 trial. Table 56 summarises the unplanned MRU cost inputs used in the cost-effectiveness model and the impact of the unplanned MRU cost has on the application of AE cost.

Table 56: Trial-based unplanned MRU costs per month

	Unplanned MRU cost, £	Source	Impact on application of AE cost
AAP	93.79	302 trial unplanned MRU	Already reflected in the trial unplanned MRU data; no need to consider additional AE cost
BSC (PP)	93.79	Assumed to be the same as PP arm of 302 trial	AE costs are included
BSC (pre-docetaxel)	93.79	Assumed to be the same as PP arm of 302 trial	AE costs are included

Docetaxel	380.29	Assumed to be the same as PP arm of 301 trial	The baseline cost of AEs was similar to that of the 301 unplanned MRU. The cost of incremental AEs were also considered in the model.
BSC (post-docetaxel)	380.29	Assumed to be the same as PP arm of the 301 trial	Treatment is similar to BSC (PP), therefore like BSC (PP) unplanned MRU, the AE costs are included
BSC (PP post-docetaxel)	380.29	301 trial unplanned MRU	Already reflected in the trial unplanned MRU data, no need to consider additional AE cost
AAP (post-docetaxel)	380.29	301 trial unplanned MRU	Already reflected in the trial unplanned MRU data, no need to consider additional AE cost
BSC (before death)	380.29	Assumed to be the same as the 301 model post-progression cost	Treatment is similar to BSC (PP post-docetaxel), therefore like BSC (PP post-docetaxel) unplanned MRU, the AE costs are included

AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.

End-of-life costs

Resource use and associated costs typically spike in the months immediately prior to death for patients with prostate cancer [250]. Because OS differs by treatment for mCRPC, the effects of discounting lead to an incremental difference in terminal costs per treatment, and thus terminal costs were considered in the economic model. The MRU of mCRPC patients over their last 3 months of life were defined based on consultation with five UK oncologists who actively treat mCRPC [61]. 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 for modelling purposes. Costs for a 1-hour home care visit in both day and evening settings (cost of weekday hour is £23, cost of weekday evening hour is £24; averages to £23.50 per hour) were obtained from the unit costs of health and social care database [206]. The daily cost of both a hospice centre and a palliative care unit of a hospital was taken to be £116 (Inpatient, Hospital Specialist Palliative Care, 19 years+, code SD03A), based on the UK National Schedule of Reference Costs 2012–2013 [156]. In summary, terminal costs based on the description above were £3,598 per patient and was applied as a one-off cost in the economic model.. This is consistent with a recent NICE appraisal for enzalutamide for the treatment of mCRPC previously treated with a docetaxel-containing regimen [251]. A cost for terminal care of £3,133 per patient was applied in the economic model.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Consideration of grade 3/4 AEs is a potential differentiating factor among different treatment regimens in the model. A statistical analysis of unplanned, event-related

MRU collected in the COU-AA-302 and COU-AA-301 trials was used to determine the baseline rate of resource utilisation for pre-docetaxel AAP, BSC (PP) and AAP (post-docetaxel) (section 7.5.6). In the absence of detailed data for the other treatment regimens, the baseline MRU for docetaxel was assumed to be equal to post-docetaxel AAP in the COU-AA-301 trial. However, the effect of varying rates of grade 3/4 AEs among these treatment regimens, along with any differences in treatment costs that might be involved, was also be considered. To address the impact of differences in AE rates associated with docetaxel, we assigned costs of treating grade 3/4 AEs. For docetaxel, cost was applied to the raw incidence rate of grade 3/4 AEs [47]. For a detailed summary of MRU analysis associated with the occurrence of AEs see appendix 19.

The costs of AEs associated with treatment for mCRPC patients were based on an advisory board composed of UK oncologists familiar with treating grade 3/4 AEs to identify resources utilised in treating such events (Robert Thomas, MD; Ian Pedley, MD; Jason Lester, MD; James Wylie, MD; and Emilio Porfiri, MD; oral communication, 19.07.11). The resource utilisation considered in the model included site of care, follow-up (if needed), and medications. Treatment of AEs could occur in an inpatient setting, a clinic as a day case, the office of a general practitioner, or an office by a nurse. 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 NHS Reference Costs, 2012–2013 [156]. Medication cost was only applied to patients who were not treated as inpatient cases to avoid double counting. The treatment cost for each AE was 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 was obtained from the BNF online. Table 57 summarises the resource utilisation required to treat each grade 3/4 AE and Table 58 presents the total costs related to the treatment of each grade 3/4 AE.

A small proportion of patients receiving chemotherapy were assumed to suffer grade 3 or 4 febrile neutropaenia, which can lead to severe outcomes. Granulocyte colony-stimulating factor (G-CSF) is an effective treatment option for febrile neutropaenia, so the cost of G-CSF was considered in the economic model. For docetaxel, both prophylactic (use of G-CSF to prevent febrile neutropaenia) and therapeutic (use of G-CSF in response to the occurrence of febrile neutropaenia) use were considered in the model. Pegfilgrastim (Neulasta®) is the G-CSF most commonly used (UK KOLs) and the percentage of patients requiring therapeutic use of G-CSF was based on the rate of febrile neutropaenia observed among patients receiving chemotherapy in a study by Tannock et al. [47], while the percentage of prophylactic G-CSF use was based on UK KOL input. In the model, the use of G-CSF is as follows: prophylactic use starts in cycle 1 for 15% of the patients and therapeutic use starts in cycle 2 for 3% of the patients.

Table 57: MRU associated with grade 3/4 AEs

	Treated as inpatient, %	Treated as oncologist clinic day case, %	Treated by GP, %	Treated by nurse visit/ phone call, %	Follow-up	Medication[a]
Neuropathy	0	100 (1–2 visits)	0	A few additional nurse visits	None	Gabapentin (900 mg t.i.d.)
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 300 µg q.d. for 1 week for 30% patients, Tazocin 4.5 g t.i.d. IV for 5 days, IV imipenem – Primaxin®[b]
Thrombocyto-paenia	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 20–40 mg q.d. (1–2 weeks), IV fluid (NaCl 0.9% IV infusion)
Hypokalaemia	50	50	0	0	1 oncologist visit	Sando-K®, IV KCl
Hypertension[d]	0	50	50	0	1 oncologist visit	Clonidine 0.1 mg orally, amlodipine 5–10 mg/day
Arthralgia	0	34	66	0	1 GP visit	OxyNorm® 5 mg every 4–6 hours, acetaminophen – paracetamol
Asthenia	0	0	0	100	No	Dexamethasone (2–4 mg) for 6 days
Diarrhoea (grade 3)[e]	50	50	0	0	1 oncologist visit for hospitalised patients	Loperamide 2 mg as needed, IV fluid
Dyspnoea[f]	N/A	N/A	N/A	N/A	N/A	N/A
Fatigue	0	0	0	100	No	Dexamethasone (2–4 mg) for 6 days
Nausea	0	100	0	0	No	Domperidone 20 mg as needed or four times a day
Vomiting	80	20	0	0	1 oncologist visit for hospitalised patients	Ondansetron 8 mg b.i.d. 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 7.5.7, 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 was observed in the COU-AA-301 trial.
[e]No grade 4 diarrhoea was observed in either abiraterone + prednisolone or mitoxantrone + prednisolone.
[f]This is rarely an isolated event, so it is treated with other events with no additional cost.
G-CSF, granulocyte colony stimulating factor; IV, intravenous; N/A, not applicable; q.d., once daily; t.i.d., three times daily.

Table 58: List of AEs and summary of costs included in the economic model

AE	Treatment cost per event, £	Medication cost[a] per event, £	Total cost per event, £
Neuropathy	553.50	7.88	561.38
Neutropaenia	808.50	0.00	808.50
Febrile neutropaenia	5,147.50	0.00	5,147.50
Thrombocytopaenia	703.80	0.00	703.80
Anaemia	945.00	233.80	1,178.80
Oedema	891.50	8.43	899.93
Hypokalaemia	1,210.50	3.75	1,214.25
Hypertension	467.50	6.83	474.33
Arthralgia	198.28	13.98	212.26
Asthenia	13.18	16.49	29.67
Diarrhoea	1,356.00	7.51	1,363.51
Dyspnoea	0.00	0.00	0.00
Nausea	693.00	2.13	695.13
Vomiting	2,033.00	9.78	2,042.78

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

Miscellaneous costs

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

None.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Structural uncertainty is addressed to a limited extent by incorporating alternative assumptions on post-docetaxel treatments into the structure of the model. The model structure has the functionality to analyse alternative post-docetaxel treatment pathways by varying the distribution of patients receiving post-docetaxel active treatment options. The model may reflect the use of docetaxel and post-docetaxel active treatment as per observations/predictions from the COU-AA-302 trial where patients in the AAP arm eligible for post-docetaxel treatment may use active treatment (e.g. cabazitaxel) for some time period before going onto BSC (before death); patients in the BSC (PP) arm may use AAP. Since cabazitaxel is not reimbursed in the UK, AAP-arm patients receive BSC (PP post-docetaxel) only after docetaxel treatment failure, and the BSC (PP)-arm patients may receive AAP (post-docetaxel) if they are eligible for active treatment.

Scenario analyses

A range of scenario analyses were conducted to assess the sensitivity of the model results to changing parameters. There was some uncertainty associated with the data collected from the MRU survey (section 7.5.4), therefore two scenario analyses were conducted on scheduled MRU cost inputs. In order to assess the sensitivity of the model results to changing utility through the treatment sequence, three scenarios appropriately manipulated utility values. The model's sensitivity to other cost variables has also been addressed as detailed below. Since the survival curves

utilised in the base case were closely fit to the COU-AA-302 trial data, additional analyses were explored in order to test the model's sensitivity to survival estimates.

Although enzalutamide is now available in the post-docetaxel setting both costs and clinical effectiveness are deemed similar to that of AA [251], supplementing one drug for the other as a post-docetaxel active treatment in the comparator arm will have no significant impact on the economic argument. In addition, there is no conclusive clinical evidence to support a clinical benefit of using enzalutamide in the post-docetaxel setting if a patient has already received AA prior to docetaxel. A scenario analysis has been conducted to explore the impact of including enzaluatamide as a treatment option in the post-chemotherapy setting.

Scenario 1: Base-case analysis without PAS
The base-case analysis implements the PAS, therefore an additional analysis was conducted to show the cost-effectiveness of AAP if the PAS was not implemented in either pre- or post-docetaxel settings.

Scenario 2: Scheduled MRU costs using urologist responses
A panel of oncologists was used to generate the MRU for the base case (section 7.5.4). This scenario explored using the urologist responses in order to test the model's sensitivity to scheduled resource use. Table 59 summarises the scheduled MRU costs, reported by urologists, as applied in the model.

Table 59: Scheduled urologist MRU costs

	Median, £	**25th percentile, £**	**75th percentile, £**
AAP	116.64	52.54	215.50
BSC (PP)	75.36	42.44	166.67
BSC (pre-docetaxel)	75.36	42.44	166.67
Docetaxel	132.64	55.57	230.63
BSC (post-docetaxel)	77.72	41.10	145.91
BSC (PP post-docetaxel)	77.72	41.10	145.91
AAP (post-docetaxel)	136.89	66.58	252.01
BSC (before death)	47.33	12.55	129.92

AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Scenario 3: Scheduled MRU costs using both oncologist and urologist responses
In an additional scenario, scheduled MRU reported by both oncologists and urologists were used and the respective costs were recalculated to account for all 103 survey responders. Table 60 summarises the scheduled MRU costs, reported by all clinicians, as applied in the model.

Table 60: Scheduled oncologist and urologist MRU costs

	Median, £	**25th percentile, £**	**75th percentile, £**
AAP	149.53	66.78	207.35
BSC (PP)	81.45	42.23	161.87
BSC (pre-docetaxel)	81.45	42.23	161.87
Docetaxel	185.94	61.43	292.48
BSC (post-docetaxel)	74.69	42.15	144.08
BSC (PP post-docetaxel)	74.69	42.15	144.08
AAP (post-docetaxel)	174.39	76.22	241.41
BSC (before death)	35.83	15.90	130.68

AAP, abiraterone acetate plus placebo; AE, adverse event; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Scenario 4: Utilities from the FACT-P to EQ-5D mapping study
The utilities from the patient utility study were substituted for the corresponding values from the trial-based FACT-P to EQ-5D mapping study [155]. The results of the mapping study, as applied in the model scenario, are detailed in Table 43 (section 7.4.4).

Scenario 5: Utilities from the mapping study applied in the post-docetaxel setting
A scenario was also explored using a mixed source of utility inputs. Utilities remained the same as the base case in the pre-docetaxel setting whilst in the post-docetaxel setting they were substituted for the corresponding values from the FACT-P to EQ-5D mapping study. Since docetaxel disutility was not captured by the mapping study the decrement was also applied in this scenario. Table 61 details the utility values used in this scenario analysis.

Table 61: Mixed-source utility scenario analysis

	Utilities		**Source**
	Mean	**SE**	
Post-ADT baseline	[redacted]	[redacted]	UK mCRPC Utility Study
AAP on-treatment utility increment	[redacted]	[redacted]	FACT-P to EQ-5D mapping study
BSC (pre-docetaxel)	[redacted]	[redacted]	UK mCRPC Utility Study
Docetaxel	[redacted]	[redacted]	UK mCRPC Utility Study
Docetaxel on-treatment disutility	[redacted]	[redacted]	FACT-P to EQ-5D mapping study
Post-docetaxel	[redacted]	[redacted]	FACT-P to EQ-5D mapping study
BSC (before death)	[redacted]	[redacted]	FACT-P to EQ-5D mapping study

Scenario 6: Utilities prior to death
The third scenario analysis around utilities involved aligning the utility for BSC (before death) with the utility used in a recent enzalutamide STA submission for this treatment phase [251]. The enzalutamide appraisal used a different utility value from the same Sandblom et al. [154] study used in the current base case. The enzalutamide appraisal applied a utility decrement for disease progression of –0.085, which represented the decrease in utility from 16 to 8 months before death to 8 to 0 months before death. Hence a BSC (before death) utility of [redacted] (i.e. [redacted]– 0.085) was applied in order to test the sensitivity of the ICER to the end-of-life stage in the model.

Scenario 7: Substituting prednisolone use with dexamethasone use
According to expert medical opinion garnered from tha Janssen Advisory Board (13.11.2012), clinical practice appears to be switching from use of prednisolone to dexamethasone. A scenario analysis was conducted to reflect the scenario in which prednisolone was substituted for dexamethasone, with a cost of £0.06 per 10mg dose, at all appropriate stages in the economic model. There is no evidence to assume difference in clinical efficacy between prednisolone and dexamethasone.

Scenario 8: Testing prediction coefficients to generate comparable survival estimates

In the model base case, the survival curves from COU-AA-302 were used to derive the prediction equations. This approach has limitations, as the number of patients still on treatment post-docetaxel in the COU-AA-302 study was small, which introduces uncertainty around the survival curves at the end stage of disease, especially when comparing treatment arms. In this scenario, treatment coefficients for the post-docetaxel phases were varied in order to generate comparable survival estimates in both AAP and BSC (PP) arms.

Scenario 9: Patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel
A scenario analysis was run to compare AAP to a BSC (PP) treatment pathway where no active treatments are available following docetaxel. The treatment pathway for patients in this alternative BSC (PP) arm is therefore:
BSC (PP) → BSC → Docetaxel → BSC→ BSC before death.
In order to achieve this model dynamic, the distribution of patients eligible for 1st-line post-docetaxel active treatments was set so that 100% received placebo in both the AAP and BSC (PP) arms.

Scenario 10: Enzalutamide included as a post-docetaxel active treatment option
Enzalutamide has recently been approved by NICE for the use in patients with mCRPC in the post-chemotherapy setting, thus an analysis was conducted in order to model the option of using enzalutamide as a post-docetaxel active treatment. In order to achieve this, the post-docetaxel treatment distribution was modelled so that 100% received enzalutamide in the AAP arm, whilst 56.2% received enzalutamide and 48.2% received AAP in the comparator arm.

Scenario 11: No restriction on patients' ECOG status when switching to docetaxel after 1st-line treatment
Current NICE recommendations are to only give docetaxel to men with mCRPC if Karnofsky PS ≥60% [147], which is approximately ECOG PS <2. This is in line with clinical experts in the UK (Murray Yule and John Frew), who have indicated that docetaxel should not be given to patients with ECOG PS ≥2. This scenario analysis removed the restriction on docetaxel use following the observation from the COU-AA-302 study that 10.1% of the 543 patients who received docetaxel as subsequent therapy (see Table 21) had ECOG PS ≥2 at the start of docetaxel treatment.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way sensitivity analysis
The model explored both structural and parameter uncertainty in a variety of ways. Key model drivers were tested through one-way sensitivity analysis.

Table 62 indicates the key parameters varied in one-way sensitivity analysis to assess the impact on model results, including model settings, overall survival, treatment compliance, MRU and utility values.

Table 62: Model parameters varied in one-way sensitivity analysis

Parameter	Base-case value	Alternate value	Justification
Model settings			
Time horizon	Lifetime	10 years	The median survival in the COU-AA-302 trial was 35.3 months for AAP (third planned interim analysis [18]). A time horizon of 10 years or longer has been used in previous economic assessments in prostate cancer and other advanced cancers [101;150]
Discount rate: health benefits	3.5%	0–5%	Recommendations of the panel on cost-effectiveness in health and medicine. Discounting may significantly impact PV of costs and health benefits when a significant difference in the timing of costs/health benefits exists
Discount rate: costs	3.5%	0–5%	
Clinical settings			
Truncation of survival curves at 1%	Yes	No	Extreme values (unreasonable estimates generated by the survival function of time spent in an activity such as treatment) may be removed /assigned the time associated with the cut-off point to enhance face validity
Distribution of 1st Line Treatment Duration	Log-logistic	Weibull alone	Log-logistic models (best fit) have long tails (resulting in extreme estimates for time on treatment), and cost-effectiveness is influenced by mean time on treatment, which is strongly influenced by the tail of the survival curve. To improve face validity of extrapolations, a different survival model (Weibull) for the long flat segment of the survival curve is applied.
		Log-logistic then Weibull beyond trial period	
Cost inputs			
First-line AA compliance	98%	95–100%	A compliance rate of 98% was reported in the COU-AA-302 trial (assumed to impact cost in the simulation)
Scheduled MRU	As per Table 55	25th–75th percentile on all scheduled MRU	The scheduled MRU used in the base case was calculated using the median therefore 25th and 75th quartiles were used to explore the upper and lower extremes of respective MRU costs
Unplanned MRU	As per Table 56	±20% on all unplanned MRU costs	The unplanned MRU used in the base case was from a single source; the COU-AA-302 trial, therefore all costs were varied ±20% to explore the extremes of plausible MRU costs
Utility inputs			
Post-ADT baseline	[redacted]	±20% [redacted]	Varied ±20% in order to reflect the extremes of plausible utility values for respective states
AAP on-treatment utility increment	[redacted]	±20% [redacted]	
BSC (pre-docetaxel)	[redacted]	±20% [redacted]	
Docetaxel	[redacted]	±20% [redacted]	
Post-docetaxel	[redacted]	±20% [redacted]	
BSC (before death)	0.500	±20% (0.4–0.6)	

AA, abiraterone acetate; AAP, abiraterone acetate plus prednisolone; ADT, androgen deprivation therapy; BSC, best supportive care; MRU, medical resource utilisation.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

The model incorporates probabilistic sensitivity analysis (PSA) to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters was characterised using probability distributions and analysed using Monte Carlo simulation (200 iterations). In PSA, the uncertainties around parameters were estimated, including coefficients of the prediction equations, costs, and utility. To introduce uncertainty in the prediction equations, Cholesky decomposition was used to correlate all the parameters within a risk equation. Importantly, this can handle correlating a high number of parameters. Table 63 indicates the specific parameters varied and the probability distributions used, and Table 64, Table 65, and Table 66 present the means and standard errors. The covariance matrices used to calculate the decomposition matrices in Cholesky decomposition are shown in appendix 16. For each parameter, the same random number was used across both treatment arms when probabilistic sensitivity analysis variations were drawn to ensure consistency.

The PSA has a couple of key limitations. First, Cholesky decomposition is used to correlate the parameters **within** the statistical equations; however, correlations **across** equations are not captured. For example, if age is assigned a higher than mean effect on the survival in one equation, it may be more likely to have higher than mean effect in another equation. But the age effects in these equations are totally independent. We may underestimate the uncertainties by not accounting for the inter-equation correlation. Another limitation is that some of the model inputs are based on KOL response, which does not allow for a good estimate of the standard error.

Table 63: Model parameters varied in the PSA

Parameter	Distribution
Parameters of the prediction equations[a]	Cholesky decomposition[b]
Utilities	Beta
Costs	
Premedication	Gamma
Administration	Gamma
Scheduled, disease-related MRU follow-up	Gamma
Unscheduled event-related MRU	Gamma
End-of-life	Gamma

[a]All predictions equations were varied in the PSA except those used to update patient characteristics (ECOG status, PSA progression, radiographic progression, opiate use).
[b]Coefficients were varied using Cholesky decomposition of the covariance matrix.
MRU, medical resource utilisation; PSA, probabilistic sensitivity analysis.

Table 64: Monthly cost parameters varied in the PSA

Parameter	Administration, £		Scheduled MRU, £		
	Mean	SE	Mean	25th percentile	75th percentile
AAP			217.22	129.24	266.77
BSC (PP)			82.40	43.56	158.26
BSC (pre-docetaxel)			82.40	43.56	158.26

Docetaxel	214.00	21.40	203.46	107.22	248.79
BSC (post-docetaxel)			116.01	47.69	159.14
BSC (PP post-docetaxel)			116.01	47.69	159.14
AAP (post-docetaxel)			198.76	96.76	223.37
BSC (before death)			39.96	21.54	124.59

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; SE, standard error; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Table 65: One-off cost parameters (£) varied in the PSA

Parameter	Monthly Unplanned MRU		Terminal	
	Mean	SE	Mean	SE
AAP	93.79	0.336	3,598.00	359.80
BSC (PP)	93.79	0.336		
BSC (pre-docetaxel)	93.79	0.336		
Docetaxel	380.29	0.105		
BSC (post-docetaxel)	380.29	0.105		
BSC (PP post-docetaxel)	380.29	0.105		
AAP (post-docetaxel)	380.29	0.105		
BSC (before death)	380.29	0.105		

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; MRU, medical resource utilisation; PP, placebo plus prednisolone; SE, standard error.

Table 66: Utility parameters varied in the PSA

Parameter	Utilities	
	Mean	SE
Post-ADT baseline	[redacted]	[redacted]
AAP on-treatment utility increment	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Post-docetaxel	[redacted]	[redacted]
BSC (before death)	0.500	0.080

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; SE, standard error.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 67 compares clinical trial results with model predictions based on the treatment pathway under the UK setting. Predicted treatment duration measures and OS were consistent with the clinical trial AAP and BSC (PP) arm results. Predicted median OS compares directly with the COU-AA-302 trial data. Median time on AAP/BSC (PP) from the model is also closely aligned with observed AAP/BSC (PP) treatment duration. Time on treatment is additionally confirmed through comparison of the percentage of patients on AAP versus BSC (PP) over time in the COU-AA-trial and model. Graphs further detailing these comparisons can be found in section 7.8

where simulated survival curves for time on treatment and OS under the trial and UK setting are compared to Kaplan–Meier curves (i.e. observed clinical trial results).

Table 67: Summary of model results compared with clinical data

Outcome	Clinical trial result (AAP vs. BSC [PP])	Model result: UK setting (AAP vs. BSC [PP])
Treatment duration of AAP/BSC (PP)		
≥ 6 months	81.0% vs. 59.6%	83.6% vs. 65.5%
≥ 12 months	55.7% vs. 34.1%	60.3% vs. 34.8%
≥ 18 months	38.4% vs. 21.7%	42.3% vs. 20.4%
≥ 24 months	28.4% vs. 14.1%	30.6% vs. 12.6%
Median	13.80 vs. 8.28 months	15.10 vs. 8.53 months
OS		
Median	35.29 vs. 30.13 months	35.11 vs. 29.68 months

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; OS, overall survival.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 68 provides a summary of the proportion of patients in the pre-docetaxel, on-docetaxel and post-docetaxel phases of the model, and the respective duration of time spent in that treatment phase.

Table 68: Summary of proportion of patients and respective duration in each treatment phase

Treatment phase	AAP		BSC (PP)	
	% in each treatment phase[a]	Mean duration (years)	% in each treatment phase[a]	Mean duration (years)
Pre-docetaxel				
1st-line active treatment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active treatment[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

*Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate + prednisolone; PP, placebo + prednisolone.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

N/A for this individual DES.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 69 summarises survival times within each phase in the model.

Table 69: Summary of Life Years gained by pre/on/post-docetaxel status

		AAP	BSC (PP)
Total LY gained		[redacted]	[redacted]
Pre-docetaxel survival (Include pre-docetaxel treatment and BSC)	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]
On-docetaxel survival	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]
Post-docetaxel survival (exclude post-docetaxel BSC)	% entered this phase	[redacted]	[redacted]
	Mean survival within this phase of those who entered the phase	[redacted]	[redacted]

AAP, abiraterone acetate + prednisolone; BSC, best supportive care; LY, life year; OS, overall survival; PP, placebo + prednisolone.

Two key points explain why the QALY gains are lower in the AAP arm versus the BSC (PP) arm in the both on-docetaxel and post-docetaxel treatment phases:

(1) BSC (PP) patients are more likely to receive docetaxel following disease progression compared to AAP patients and have longer duration with docetaxel and post-docetaxel treatment
   - AAP-arm patients spend more time on 1st-line treatment (receiving benefit) and are less likely to move on to docetaxel

(2) BSC (PP) patients are allowed to receive post-docetaxel AAP whilst AAP patients can only receive BSC after they fail docetaxel, which leads to the difference in post-docetaxel QALYs
   - The active treatment-eligible group in the AAP arm who do not take post-docetaxel active treatment in the model follow the same survival observed in the COU-AA-302 trial with a 'negative' treatment (see section 7.3.1 and Figure 13 for further details) applied in the time to post-docetaxel active treatment discontinuation equation based on 301 data.
   - In the COU-AA-301 trial, patients with only one prior line of therapy benefited more from AAP than those with 2+ lines of therapy. By the time AAP patients are eligible for docetaxel they have already received one line of therapy. The same pattern is observed in the post-docetaxel phase.

The accrued QALYs are provided in section 7.7.5.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost.

Table 70: Summary of QALY gain by pre/on/post-docetaxel status

	AAP	BSC (PP)	Increment	Absolute Increment, %
Total QALYs	[redacted]	[redacted]	**0.57**	100
Pre-docetaxel QALYs	[redacted]	[redacted]	0.71	124.6
On docetaxel QALYs	[redacted]	[redacted]	–0.10	17.5
Post-docetaxel QALYs	[redacted]	[redacted]	–0.04	7.0

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; QALY, quality-adjusted life year.

Results show that the majority of the QALY gain in the AAP arm is captured in the pre-docetaxel setting, corresponding to the significantly extended duration of time on first-line active treatment when compared to BSC (PP). Similar proportions of patients spend similar durations of time on docetaxel, experiencing comparable QALY gains and incurring comparable costs in both treatment arms. In the post-docetaxel phase, the AAP arm has a lower QALY gain, as experienced by the PP arm in both the COU-AA-301 and COU-AA-302 trials, whereby patients spend very little time on any subsequent active treatment and consequentially longer on BSC before death.

Table 71: Summary of costs by health state disaggregated by category of cost

	AAP, £	BSC (PP), £	Incremental, £	Absolute increment, %
Pre-docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Drug, premedication, and administration	[redacted]	[redacted]	[redacted]	[redacted]
Incremental grade 3/4 AEs	[redacted]	[redacted]	0	0.0
Unplanned, event-related MRU	[redacted]	[redacted]	1,159	3.7
Scheduled, follow-up MRU	[redacted]	[redacted]	1,185	3.8
Terminal	[redacted]	[redacted]	142	0.5
On and post-docetaxel	[redacted]	[redacted]	**–4,960**	100
Drug, premedication, and administration	[redacted]	[redacted]	–3,378	68.1
Incremental grade 3/4 AEs	[redacted]	[redacted]	–21	0.43
Unplanned, event-related MRU	[redacted]	[redacted]	–960	19.4
Scheduled, follow-up MRU	[redacted]	[redacted]	–381	7.7
Terminal	[redacted]	[redacted]	–220	4.4

Results indicate that the majority of incremental costs ([redacted]) are attributed to AAP medication and administration in the pre-docetaxel setting. A cost decrement of [redacted] is apparent in the on/post-docetaxel stage of mCRPC when comparing AAP to BSC (PP).

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Base-case analysis with PAS

In the base-case analysis, the estimated ICER for AAP vs. BSC (PP) is £46,722, based on incremental costs of £26,404 and incremental QALYs of 0.57. Although costs associated with the implementation of AAP were substantially greater, the base-case analysis generated an incremental life year gain of 0.62 as illustrated in Table 72 (increased from [redacted] years to [redacted] years) resulting in a cost per life year gained of £42,492. These ICERs are similar to those approved by NICE in the post-chemotherapy STA appraisal.

Table 72: Base-case results (with PAS)

Technology	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.57	46,722

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

End-of-life consideration

ICERs in the base case were similar to other cancer drugs recommended by NICE that have met end-of-life criteria. The case for AA to be considered by NICE under the policy on appraising life-extending, end-of-life medicines is presented below [39]:

1) **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**
   The prognosis of mCRPC patients is poor. Five-year survival rates of only 26–31% have been reported [40-42]. The control arm of the COU-AA-302 study shows that asymptomatic and mildly symptomatic patients have a short life expectancy of approximately 30 months; however patients in the trial are likely to have gone on to receive other clinical trial technologies post-docetaxel and therefore the survival observed for these patients is probably not reflective of the average mCRPC patient in the UK. The EAU [38] has estimated that the mean survival of patients with asymptomatic disease, dependent on the extent of metastases, is 9–27 months which is indicative that average survival is within the range considered end-of-life criteria (Table 6). As the disease becomes symptomatic, survival time decreases accordingly. For example, patients in docetaxel trials only have a median OS of 18–22 months [43].

2) **There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment**
   AAP offers the asymptomatic and mildly symptomatic patient population a 5.2-month increase in median OS compared to BSC with PP [18] which exceeds the survival benefit observed for patients given AAP in the post-docetaxel setting (4.6 months) [85]. Patients now have the opportunity to receive AAP earlier in the course of their disease (i.e. post-ADT, pre-chemotherapy rather than post-chemotherapy). If patients receive AAP earlier in their disease, they not only gain additional survival but are also able to preserve their HRQL earlier in the disease process, rather than extending their life at a time when they are likely to have a poorer HRQL.

3) **The treatment is licensed or otherwise indicated, for small patient populations**
   It is estimated that in 2014, 4,689 patients in England and Wales will have asymptomatic or mildly symptomatic mCRPC post-ADT, pre-chemotherapy (see sections 2.2 and 8). A further 2,483 patients are estimated to be eligible for AAP in the post-chemotherapy setting (section 2.2). Now that AAP is available to patients in the post-ADT, pre-chemotherapy setting it is anticipated that the number of patients receiving treatment in the post-chemotherapy setting will drop in future years, as those who have received AAP in the post-ADT, pre-chemotherapy setting will not be eligible for treatment post-chemotherapy. Once this is

accounted for, the total number of patients eligible for treatment with AAP across both indications will remain small; estimated at 7,172 patients in 2014

The model demonstrates that introducing AAP at an earlier line of therapy (post-ADT, pre-chemotherapy) provides the NHS in the UK with a cost-effective treatment when compared to the very limited BSC treatment options that asymptomatic and mildly symptomatic mCRPC patients currently receive.

Sensitivity analyses

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

The results of one-way sensitivity analysis are presented in Table 73, showing the lower and upper ICER limits generated by the simulation model using the PAS base case. Model settings were consistently set using a sampling method of 10 trial replications to ensure the most stable results. The accompanying tornado diagram is shown in Figure 15 which also includes a sensitivity analysis in which the discount rate applied to health benefits and costs were varied simultaneously over a 0–5% range. Results show the impact on the ICER to range from £43,248 to £48,258/QALY. Please note that the tornado diagram contains a wider range of parameters to that in the active Excel cost-effectiveness model due to the complexity of the computational demand.

The majority of cases within the deterministic sensitivity analyses indicated that the results were relatively stable across a range of assumptions. The model was most sensitive to post-ADT baseline utility, discounting, 1st-line treatment duration and a shorter time horizon. Within most of the assumptions tested, ICERs for AAP were similar to other oncology products that have been accepted by NICE under end-of-life criteria, coming under £50,000/QALY gained at the upper ICER limit. See Figure 43 in appendix 20 for the respective tornado diagrams for the base-case scenario in which the PAS was not applied.

The deterministic analysis suggested that different wide variation to MRU (scheduled and unscheduled) had a limited impact on cost-effectiveness; in the sensitivity analysis varying these parameters from base case altered the ICER range for AAP vs. PP to £46,163–47,750/QALY. Post-ADT baseline utility had the largest impact on cost-effectiveness, however due to the fact that these utility values are derived from a UK-based patient utility study and the fact that they are closely aligned with values from the Sandblom study [154] and NICE TA 259 [15], there is a high degree of certainty that the true progression-free utility for this population is close to the [redacted] used in the model.

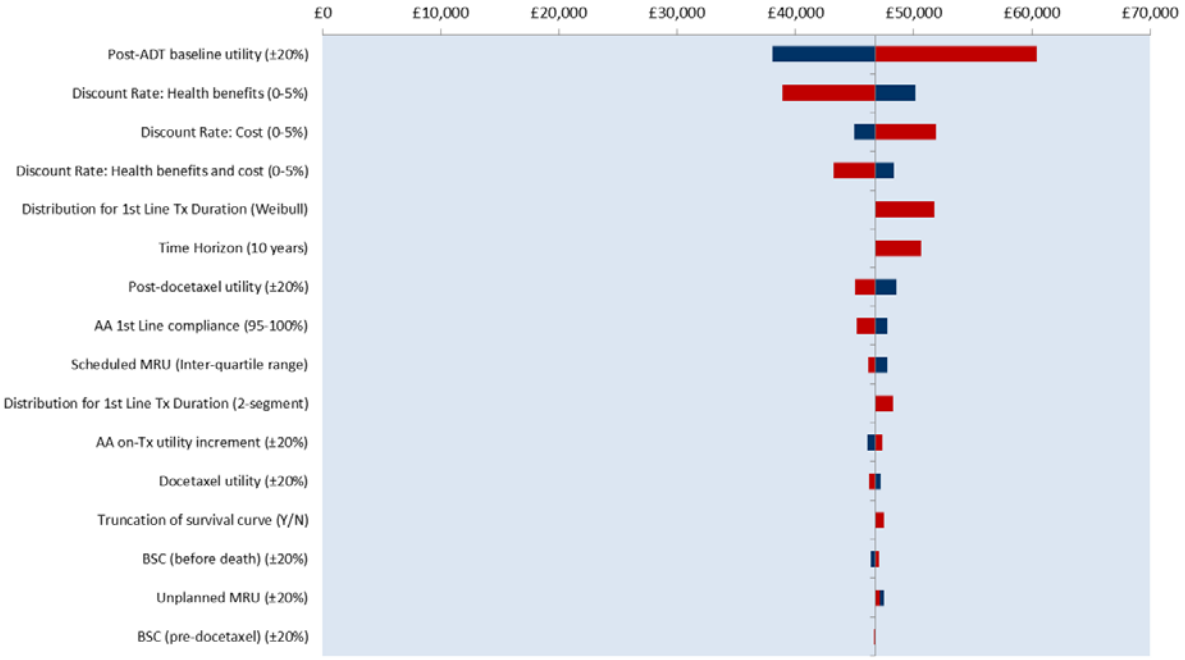
Table 73: One-way sensitivity results

	Base-case parameter	Proposed variation	ICER, £/QALY
Model base-case ICER			**46,722**
Model settings			
Time horizon	Life time	10 years	50,622
Discount rate: health effects	3.5% for health effects & costs	0–5% for health effects 3.5% for costs	38,921–50,166
Discount rate: costs	3.5% for health	3.5% for health effects	45,006–51,915

	effects & costs	0–5% for costs	
Discount rate: for health effects & costs	3.5% for health effects & costs	0–5% for health effects & costs	43,248–48,324
Clinical settings			
Truncation of OS curve at 1%	Truncated	Non-truncated	47,519
Distribution for 1st-line treatment duration	Log-logistic (best fit)	Weibull only	51,776
		2-segment curve	48,268
Cost inputs			
AA 1st-line compliance	98%	95–100%	45,159–47,763
Scheduled MRU	As per MRU study	25th–75th percentile on all scheduled MRU	46,163–47,750
Unplanned MRU	As per COU-AA-302 trial	±20% on all unplanned MRU costs	47,126–47,504
Utility inputs			
Post-ADT baseline	[redacted]	±20% [redacted]	38,087–60,418
AA on-treatment utility increment	[redacted]	±20% [redacted]	46,096–47,364
BSC (pre-docetaxel)	[redacted]	±20% [redacted]	46,674–46,769
Docetaxel	[redacted]	±20% [redacted]	46,245–47,208
Post-docetaxel	[redacted]	±20% [redacted]	45,052–48,519
BSC (before death)	0.500	±20% (0.4–0.6)	46,345–47,104

The tornado diagram in Figure 15 also includes a sensitivity analysis in which the discount rate applied to health benefits and costs were varied simultaneously over a 0–5% range. Results show the impact on the ICER to range from £43,224 to £48,258/QALY. Please note that the tornado diagram contains a wider range of parameters to that in the active Excel cost-effectiveness model due to the complexity of the computational demand.

Figure 15: Tornado diagram with PAS

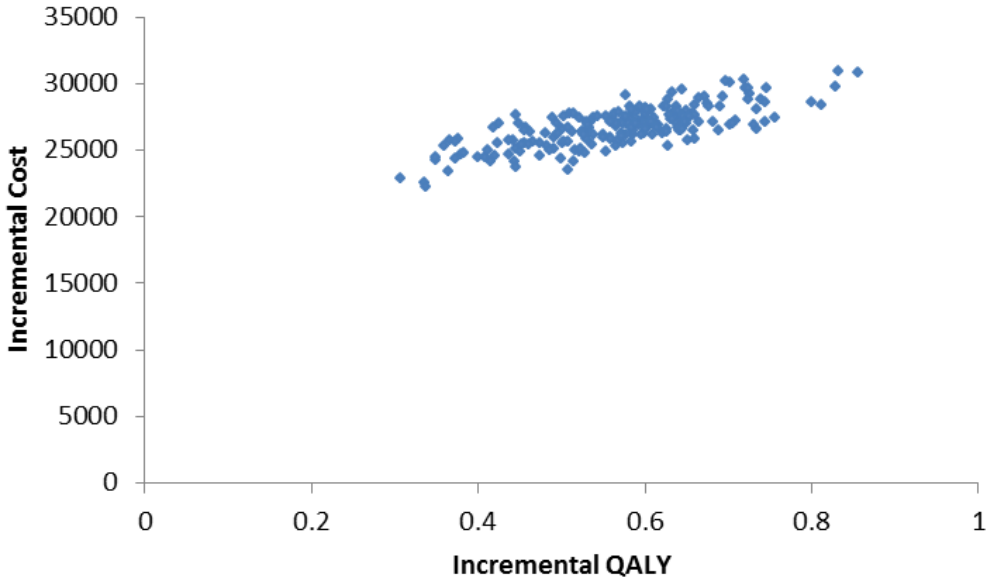


AA, abiraterone acetate; ADT, androgen deprivation therapy; BSC, best supportive care; MRU, medical resource utilisation; N, no; PAS, patient access scheme; Tx, treatment; Y, yes.

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

PSA for the base case with the PAS is presented in Figure 16. See Figure 44 in appendix 20 for the respective PSA scatter plot for the base-case scenario in which the PAS is not applied. The PSA for the PAS base case is summarised in Table 74. At a QALY threshold of £50,000, the probability that AAP is the most cost-effective option when compared to BSC (PP) is 39%; and at a QALY threshold of £55,000, the probability increases to 67%. The cost-effectiveness acceptability curve shown in Figure 17 shows the probability of cost-effectiveness over a range of willingness-to-pay thresholds.

Figure 16: Cost-effectiveness scatter plot with PAS



PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 17: Cost-effectiveness acceptability curve with PAS

BSC, best supportive care; PAS, patient access scheme.

Table 74: Summary of the PSA for the base case with PAS

WTP threshold	AAP, %	BSC (PP), %
£40,000/QALY	0	100
£45,000/QALY	10	89
£50,000/QALY	38	63
£55,000/QALY	67	34

QALY, quality-adjusted life year.

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

Scenario 1: Base-case analysis without PAS

A scenario in which the PAS was not applied within the economic model is presented as an alternative to the base-case analysis in Table 75. In this analysis the estimated ICER for AAP vs. BSC (PP) is £[redacted], based on incremental costs of £[redacted] and incremental QALYs of [redacted].

Table 75: Results of base case without PAS

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 2: Urologist scheduled MRU costs

The results of using urologist scheduled MRU costs in the model instead of the oncologist scheduled MRU cost used in the base-case analysis are presented in Table 76. The resulting ICER is lower than that of the base-case analysis which reflects the lower resource use reported by urologists compared to oncologists [248].

Table 76: Results when using scheduled urologists MRU costs

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,191	0.62	0.57	46,344

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 3: Oncologist and urologist scheduled MRU costs

The results of using the oncologist and urologist scheduled MRU combined costs in the model, instead of the oncologist scheduled MRU cost alone used in the base-case analysis, are presented in Table 77. The resulting ICER is lower than that of the base-case analysis which reflects the differing MRU costs recalculated when resource use reported from all 103 clinicians were combined.

Table 77: Results when using combined oncologist and urologist scheduled MRU costs

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,267	0.62	0.57	46,480

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 4: Utilities from the FACT-P to EQ-5D mapping study
Utilities from the patient utility study were replaced by respective values from the FACT-P to EQ-5D mapping study. Results presented in Table 78 indicate that this source of utilities is associated with a moderate increase in the ICER.

Table 78: Results when using FACT-P to EQ-5D mapping utility values

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.54	50,163

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 5: Utilities from the FACT-P to EQ-5D mapping study applied post-docetaxel
Results generated by substituting utility values from the Patient Utility Study for corresponding values from the FACT-P to EQ-5D mapping study in the post-docetaxel setting are presented in Table 79. Results confirm that utility values do not act as a major driver of the model outcomes.

Table 79: Results when using utilities from the FACT-P to EQ-5D mapping study post-docetaxel

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.58	46,114

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 6: Utilities prior to death
A utility value of [redacted] was utilised for BSC (before death) aligned to the same source used in the STA of enzalutamide. Results from this scenario are presented in Table 80. The decrease in the ICER reflects the effect of capturing a greater proportion of utility from those patients in the AAP arm spending a duration of [redacted] years in the final BSC (before death) state.

Table 80: Results when utility of BSC before death is 0.615

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.57	46,289

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 7: Substituting prednisolone use with dexamethasone use in BSC
The cost of prednisolone was appropriately substituted for the cost of dexamethasone in the model as per aforementioned expert medical opinion. The results presented in Table 81 show little impact on the overall ICER.

Table 81: Results of substituting the cost of prednisolone with dexamethasone

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,521	0.62	0.57	46,929

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 8: Testing prediction coefficients to generate comparable survival estimates

Varying the prediction equations used to derive the post-docetaxel survival estimates impacted the patient flow through the simulation model. Table 82 shows how the distribution of patients changes as a result of altering coefficients to generate comparable survival estimates in both the AAP and BSC (PP) arms.

Table 82: Results when AAP/BSC (PP) patient distributions post-docetaxel are comparable

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	26,557	0.64	0.59	45,393

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Table 83: Impact of implementing scenario 8 on the distribution of patients in the model

	AAP		BSC (PP)	
	% in each Tx phase[a]	Mean duration (years)	% in each Tx phase[a]	Mean duration (years)
Pre-docetaxel				
1st line active Tx	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active Tx[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

[a]Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate plus prednisolone; PP, placebo plus prednisolone; Tx = treatment.

Scenario 9: Patients in the BSC (PP) arm do not receive an efficacious active treatment post-docetaxel

100% of patients who were eligible for 1st line post-docetaxel active treatment were to receive placebo in both the AAP and BSC (PP) arms. Results shown in Table 84 aimed to capture a scenario in which no active treatment is implemented in the treatment sequence post-docetaxel.

Table 84: Results when patients in BSC (PP) arm do not receive efficacious active treatment post-docetaxel

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	29,039	0.66	0.59	48,833

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 10: Enzalutamide included as a post-docetaxel active treatment option

In this scenario, enzalutamide was included as a post-docetaxel active treatment in all patients who received AAP pre-docetaxel and in 56.2% of those who received BSC (PP) pre-docetaxel.

Table 85: Results of including enzalutamide as a post-docetaxel active treatment

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	28,060	0.63	0.58	48,546

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PP, placebo plus prednisolone; QALYs, quality-adjusted life years.

Scenario 11: No restriction on patients ECOG status when switching to docetaxel after 1st-line treatment

Docetaxel is generally only recommended for men with ECOG PS <2, but this scenario removed the restriction on docetaxel use following the observation from the COU-AA-302 study that 10.1% of patients who went on to receive docetaxel had ECOG PS ≥2.

Table 86: Results when no restriction on ECOG status when switching to Docetaxel after 1st line treatment

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	£26,009	0.57	0.54	£48,146

Summary

Excluding the scenario in which the PAS was not applied, the only scenario to increase the ICER to above £50,000/QALY was that in which the the mapping study was used instead of the patient utility study (£50,163/QALY). All other scenarios resulted in ICERs of £45,393–48,833/QALY.

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

The model base-case ICER is £46,722/QALY gained and extensive sensitivity and scenario analyses demonstrate that the ICER is very stable to variation in model parameters with a higher degree of uncertainty. Within most of the assumptions tested, ICERs for AAP vs. BSC (PP) were similar to other oncology products that

have been accepted by NICE under end-of-life criteria, coming under £50,000/QALY gained at the upper ICER limit.

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

The key drivers of cost-effectiveness are pre-docetaxel utility, discounting, 1st-line treatment duration and a shorter time horizon. Variation in the parameters associated with a degree of uncertainty (scheduled and unscheduled MRU) only had a small impact on the ICER. In contrast, parameters that had a larger impact on the ICER (such as pre-docetaxel utility and duration of 1st line treatment) are underpinned by robust data extracted from the clinical trial COU-AA-302 and the bespoke UK patient utility study.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

External review
The model approach and structure were reviewed by UK clinicians. Clinicians indicated that the UK scenario treatment pathway reflected the current practice in UK. The method of using mapping algorithms to convert trial-collected FACT-P data into EQ-5D has been accepted in the NICE submission for AAP as a post-docetaxel treatment [15]. UK clinicians also provided constructive feedback on the scheduled (i.e. disease-related) follow-up-related MRU for the average patient with mCRPC.

Internal review
The basic concept of the model design was presented to an internal peer review board comprised of senior scientists who are familiar with prostate cancer. The purpose of the review was to ensure that the model was being designed correctly and rigorously from the perspective of clinical face validity and design validity. This process helped to ensure that the model design was grounded with an appropriate clinical basis.

After model programming and prior to determining final results, the completed Microsoft Excel model was verified by a modelling expert not involved in this study. A structured walk-through of the simulation was conducted to verify the logical structures in the simulation, mathematical expressions, and sequence of computations. Patients were followed from start to end of the simulation run with their event list, and profiles evaluated after each event occurred to ensure that the correct event sequences were initialised. Expressions were verified by comparing the simulated values to hand calculations. A variety of stress tests were performed to ensure that the model results were reflective of the inputs entered. The behaviour of the model under extreme-value analysis was observed, and predictions were compared against results expected from a properly functioning model. In situations where actual results diverged from the expected results, debugging was performed to investigate and remedy the discrepancy.

Comparing the model prediction versus trial observation
Once the team was confident that the model performed as intended, predictive validity was performed by comparing simulated survival curves (e.g. time on treatment, OS) with observed clinical trial data (i.e. Kaplan–Meier survival curves). To generate predictions, patient profiles from the COU-AA-302 trial (the analysed 902 patients) were used in the simulation to inform baseline patient characteristics. Each patient profile was simulated 10 times to predict individual treatment pathways. Model predictions including time to AAP/BSC (PP) discontinuation, time from AAP/BSC (PP) to docetaxel start, time from docetaxel start to docetaxel end, and OS were plotted against the Kaplan–Meier survival curves. Graphs of the key outcomes validated are shown in Figure 18 to Figure 22. In Figure 21, predicted OS is based on the treatment pathway observed (i.e. patients in the AAP arm were allowed to take post-docetaxel active treatment) from the COU-AA-302 trial. Figure 22 compares predicted OS under the UK setting (i.e. all AAP arm patients received BSC post-docetaxel, and patients with ECOG ≥2 at the end of AAP/BSC (PP) did not receive docetaxcel) versus observed OS from COU-AA-302 trial. These figures show that model predictions were consistent with the COU-AA-302 trial results. Please also see Table 67.

[redacted] 18 [redacted]
AA, abiraterone acetate plus prednisolone; BSC, best supportive care; OBS/obs, observed; Placebo, placebo plus prednisolone; PP, placebo plus prednisolone; SIM/sim, simulation; trtp, treatment arm; TTDISC1, time to discontinuation 1.

[redacted] 19 [redacted]
AA, abiraterone acetate plus prednisolone; BSC, best supportive care; OBS/obs, observed; Placebo, placebo plus prednisolone; PP, placebo plus prednisolone; SIM/sim, simulation; trtp, treatment arm; TTDOX, time to docetaxel.

[redacted] 20 [redacted]
AA, abiraterone acetate plus prednisolone; OBS/obs, observed; Placebo, placebo plus prednisolone; SIM/sim, simulation; trtp, treatment arm; TTDISC2, time to 2nd discontinuation.

[redacted] 21 [redacted]
AAP, abiraterone acetate plus prednisolone; KM, Kaplan–Meier; OS, overall survival; PP, placebo plus prednisolone.

[redacted] **22** [redacted]
KM, Kaplan–Meier; AAP, abiraterone acetate plus prednisolone; OS, overall survival; PP, placebo plus prednisolone.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Two subgroup analyses was undertaken, of patients with baseline BPI question #3 of 0 or 1 (accounting for 67% of the COU-AA-302 trial population) and of patients with ECOG PS = 0 (76% of COU-AA-302). These subgroups were prespecified in the

SAP, and the scope questioned whether AAP is likely to be more effective in asymptomatic or mildly symptomatic men. Further, these were subgroups where AAP demonstrated better efficacy in terms of OS HR compared to the ITT population (Figure 23 and Figure 24).

The subgroup analyses were pre-programmed in the model on COU-AA-302 trial patients. These patient characteristics were also included as predictors in the prediction equations. The observed difference between subpopulations is clinically meaningful and practical in that BPI and ECOG PS assessments are easily assessable in clinical routine and daily practice and can be validated based on COU-AA-302 data.

[redacted]

SOURCE: reanalysis of existing data.
AA, abiraterone plus prednisone/prednisolone; ALL, all patients; BPI, brief pain inventory; OS, overall survival; PL or PP, placebo plus prednisone/prednisolone; SE, standard error.

[redacted]

SOURCE: reanalysis of existing data.
AA, abiraterone plus prednisone/prednisolone; ALL, all patients; BPI, brief pain inventory; Ecog, Eastern Cooperative Oncology Group; OS, overall survival; PL or PP, placebo plus prednisone/prednisolone; SE, standard error.

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

Patient characteristics for the BPI #3 0–1 and ECOG 0 subgroups are shown in Table 87. Subsequent therapies, utilities, AEs and MRU were all assumed to be the same in both subgroup as in the ITT population. Analyses were conducted to explore the utility values based on the UK patient utility study for the BPI #3 0–1 and ECOG 0 subgroups (see section 7.4.3 and Table 41 for further details). The MRU analysis in the ITT population was based only on the UK patients in the trial, and further sub-setting data to these specific subgroups would lead to a very small sample size. Therefore, a conservative approach was taken to assume the same MRUs as in the overall patients.

Table 87: Characteristics of subgroups in COU-AA-302 with BPI #3 0–1 or ECOG PS 0 (55% data cut)

	BPI #3 0–1		ECOG PS 0	
	AAP (N=370)	PP (N=346)	AAP (N= 413)	PP (N= 409)
Age, years, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis, years, median	[redacted]	[redacted]	[redacted]	[redacted]
PSA, ng/mL, median	[redacted]	[redacted]	[redacted]	[redacted]
Alkaline phosphatase, IU/L, median	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin, g/dL, median	[redacted]	[redacted]	[redacted]	[redacted]
Lactate dehydrogenase, IU/L, median	[redacted]	[redacted]	[redacted]	[redacted]
FACT-P total score,	[redacted]	[redacted]	[redacted]	[redacted]

mean				
ECOG 0, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ECOG 1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
BPI #3 0–1, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
BPI #3 2–3, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Gleason score ≥8, n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Gleason score ≤7, n (%)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Bone metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Soft tissue or node metastases, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

SOURCE: reanalysis of existing data.
BPI, Brief Pain Inventory; ECOG, Eastern Cooperative Oncology Group; PS, performance status;
[a]Data missing in 30 AAP and 29 PP patients in the ECOG 0 subgroup.
[b]Data missing in 39 AAP and 23 PP patients in the BPI #3 0–1 subgroup; 42 AAP and 24 PP patients in the ECOG 0 subgroup.

7.9.3 Please describe how the statistical analysis was undertaken.

The HRs within the BPI #3 0–1 and ECOG PS subgroups were estimated using non-stratified Cox proportional hazard models. Results from these analyses were considered consistent with the primary analysis as the 95% CIs for the HRs within the subgroups included the point estimate for the primary analysis (see Figure 7 and Figure 8).

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Table 88: Subgroup BPI #3 0–1 analysis results (post-ADT baseline utility = [redacted])

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY vs. baseline	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	29,907	0.75	0.71	–4,652	42,035

BPI, Brief Pain Inventory; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 89: Subgroup ECOG PS 0 analysis results (post-ADT baseline utility = [redacted])

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY vs. baseline	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]	–	–	–	–	–
AAP	[redacted]	[redacted]	[redacted]	27,431	0.62	0.65	–4,450	42,237

ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PS, performance status; QALYs, quality-adjusted life years.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

No.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

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

However, the model shows that AAP is equally cost-effective in the post-ADT, pre-chemotherapy setting (when patients are at an earlier disease stage) than in the NICE-approved post-chemotherapy setting (when patients are at a later stage) (i.e. £46,722/QALY post-ADT, pre-chemotherapy vs £46,800/QALY post-docetaxel [15]). Given the existing funding arrangements for AAP in the post-chemotherapy setting, these results present clinicians with the option for earlier use of AAP without having to use docetaxel first. This is key, as patients will be able to benefit from AAP prior to being exposed to the potential toxicities associated with docetaxel at an earlier stage of their disease, when they are fitter and healthier.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

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

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

Strengths
One of the core strengths is that the data populating all phases of the model are derived directly from the COU-AA-302 study. The COU-AA-302 study is a robust trial with a long follow-up period (27.1 months) against the comparator of interest in the UK setting. The most recent interim analysis time point was used so that data from the largest proportion of patients could be captured. At this analysis point (just after the study was unblinded), very few patients (n=3) had crossed over from the PP arm to active treatment with AAP.

The cost-effectiveness model was developed using established DES methodology that has previously been used in HTA submissions for other late advanced and metastatic cancers (e.g. revlimid for multiple myeloma and rituximab for follicular lymphoma).

Scheduled MRU data was extracted directly from surveys of UK clinicians, and the patient utility study was a UK study conducted specifically for the purpose of UK HTA submissions.

The UK mCRPC patient utility study, which was conducted specifically for this application, provided robust utility values with which to populate the model. The

study methods, measures and other materials were designed to follow methodological requirements for inclusion of resulting study data in this submission. Validated measures used in this study offered two methods for calculating utility data, including the preferred method for meeting the NICE reference case (EQ-5D). Validated cancer and prostate cancer specific HRQL measures also captured additional detail of HRQL impact of mCRPC for evaluation of variation in impact across the course of treatment and disease progression.

Extensive deterministic and PSAs 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. A major strength of the model is the robustness of the ICER to the sensitivity analyses. Deterministic and PSAs almost consistently resulted in ICERs <£50,000/QALY vs. BSC (PP). In addition, the model approach and structure were reviewed by UK clinicians. Clinicians indicated that the UK scenario treatment pathway reflected the current practice in UK.

Limitations

A limitation of the economic analysis concerns the scheduled and unplanned MRU costs implemented in the model. A UK resource use survey was conducted to estimate the scheduled MRU associated with treating mCRPC at different stages of the disease. While this method is considered to be more reliable and robust than simple individual expert interviews, UK patient level data would have been more robust. To account for this, uncertainty in cost estimates was explored in both univariate sensitivity analyses and several scenario analyses and it is reassuring that the model was not sensitive to variations in MRU costs.

As the trial did not capture unplanned-event related MRU data specific to BSC (pre-docetaxel), docetaxel and BSC (post-docetaxel), assumptions have been made regarding costs. Since patients on BSC (pre-docetaxel) are most comparable to those on BSC (PP), the same unplanned event-related MRU was applied to this group. For docetaxel, it was assumed that baseline resource utilisation was equivalent to the placebo arm of the COU-AA-301 trial and any incremental cost difference was caused by grade 3/4 AEs. BSC (post-docetaxel) was also assumed to have similar unplanned event-related MRU as the placebo arm of the COU-AA-301 trial. Since patients in the docetaxel and the BSC (post-docetaxel) phases are symptomatic, it is reasonable to assume that the respective MRU are similar. Patients who switch to BSC (before death) are assumed to incur similar levels of unplanned event-related cost regardless of their prior treatment history. However, MRU cost data was not collected for this disease stage, therefore the respective MRU from patients in the COU-AA-301 trial was used as proxy for BSC before death.

The PSA also had some limitations. Firstly, Cholesky decomposition was used to correlate the parameters within the statistical equations, yet correlations across equations were not captured. For example, if age is assigned a higher than mean effect on the survival in one equation, it may be more likely to have a higher than mean effect in another although the age effects in these equations are totally independent. Uncertainties may be underestimated by not accounting for the inter-

equation correlation. Lastly, some of the model inputs were based on KOL response which does not permit a good estimate of the standard error.

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

In the future, once the COU-302-AA trial data become more mature, the economic evaluation could be repeated using OS derived from the trial.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

In 2006, NICE estimated that there were 10,448 men with mCRPC in England and Wales; 0.0195% of the population [33]. Using 2014 population estimates [34], this equates to 11,085 men, and this could be expected to increase to 11,341 in 2018.

Patients eligible for AAP in the post-ADT, pre-chemotherapy setting
Clinical opinion estimates that 40% of the mCRPC population will receive treatment with docetaxel in 2014 [35], which equates to 4,434 men in 2014. This estimate is aligned with a recent publication, highlighting that the number of men receiving chemotherapy increased from 11% in 2002 to 33% in 2008 within the Thames Valley Cancer Network [36]. The remaining 60% of patients (6,651) are assumed to be chemotherapy-naïve. Of these 6,651 patients, it is estimated that 70.5% [37] are asymptomatic or mildly symptomatic. Therefore, in 2014, it is estimated that there will be 4,689 men with mCRPC in whom ADT has failed who are asymptomatic or mildly asymptomatic and who do not yet require chemotherapy. Therefore, for the therapeutic indication covered by this submission, it is estimated that 4,689 men will be eligible for treatment in 2014. Table 90 contains the estimated number of patients eligible for AAP in the post-ADT, pre-chemotherapy setting.

Subgroups
BPI-SF #3 0–1
A subgroup of interest identified in the COU-AA-302 trial are those patients with a BPI #3 score of 0–1. At baseline in the COU-AA-302 trial, 66.7% of patients had a BPI-SF #3 OF 0-1. This figure is similar to that seen in the UK mCRPC utility study (section 7.4.3) in which 62% of patients had a BPI-SF#3 0-1. Applying this percentage to the number of patients in England and Wales who are asymptomatic or mildly symptomatic and chemotherapy-naïve, we can estimate the number of patients with a BPI #3 of 0–1. In 2014, it is estimated that this patient cohort will be 2,907 and could increase to 2,987 by 2018. Table 90 provides the estimated number of patients with a BPI #3 0–1 who would be eligible for treatment with AAP.

ECOG 0
Another subgroup of interest identified in the COU-AA-302 trial are those patients with a ECOG score of 0. In the UK mCRPC Utility study (section 7.4.3), 46% of the asymptomatic and mildly symptomatic chemotherapy-naïve patients had an ECOG score of 0. Applying this percentage to the number of patients in England and Wales who are asymptomatic or mildly symptomatic and chemotherapy-naïve, we can estimate the number of patients with a ECOG score of 0 in England and Wales. In

2014, it is estimated that this patient cohort will be 2,157 and could increase to 2,216 by 2018. Table 90 provides the estimated number of patients with an ECOG score of 0 who would be eligible for treatment with AAP.

Table 90: Patients eligible for treatment with AAP in the post-ADT, pre-chemotherapy setting

	2014	**2015**	**2016**	**2017**	**2018**
Population of England and Wales	56,784,200	57,175,600	57,567,00	57,958,400	58,349,800
Estimated number of mCRPC patients	11,085	11,161	11,238	11,314	11,391
Chemotherapy-naïve	60%	60%	60%	60%	60%
Number chemotherapy-naive	6,651	6,697	6,743	6,789	6,834
Asymptomatic or mildly symptomatic	70.5%	70.5%	70.5%	70.5%	70.5%
Eligible patient population	**4,689**	**4,721**	**4,754**	**4,786**	**4,818**
Subgroup BPI #3 0–1					
No. of patients with BPI #3 0–1 (62%)	2,907	2,927	2,947	2,967	2,987
Subgroup ECOG 0					
No. of patients with ECOG 0 (46%)	2,157	2,172	2,187	2,202	2,216

Patients eligible for AAP in the post-chemotherapy setting

Of the 4,434 mCRPC patients estimated to receive docetaxel in 2014, approximately 70% would be eligible for treatment with AAP in the post-chemotherapy setting, which equates to 3,104 men. The 70% accounts for patients who may die on docetaxel treatment, may have rapid deterioration on docetaxel (not suitable for further treatment) or those men in whom AAP may be contraindicated or unsuitable. Four oncologists were consulted to estimate the percentage of patients who would be eligible for AAP following treatment with docetaxel. The responses varied from 55% to 85% (individual responses are collated in appendix 1) and, therefore, we assumed the midpoint of 70% of patients would be eligible for treatment with AAP. Therefore, for the indication of AAP post-docetaxel, it is estimated that 3,104 men will be eligible for treatment in 2014.

As mCRPC patients will be treated earlier in the patient pathway with AAP it is assumed that the number of patients eligible for treatment with AAP in the post-chemotherapy setting will decline as patients who receive AAP in the post-ADT, pre-chemotherapy setting are not eligible for AAP re-treatment post-chemotherapy. It is estimated that the eligible patient pool for treatment with AAP post-chemotherapy will decline to 1,361 by 2018. Table 91 contains the estimated number of patients eligible for AAP in the post-chemotherapy setting before and after the introduction of AAP in the post-ADT, pre-chemotherapy setting.

Table 91: Patients eligible for treatment with AAP in the post-chemotherapy setting

	2014	2015	2016	2017	2018
Population of England and Wales	56,784,200	57,175,600	57,567,00	57,958,400	58,349,800
Estimated number of mCRPC patients	11,085	11,161	11,238	11,314	11,391
Receive docetaxel	40%	40%	40%	40%	40%
Number receiving docetaxel	4,434	4,464	4,495	4,526	4,556
Assume 70% of these are eligible for AAP post-docetaxel	3,104	3,125	3,147	3,168	3,189
Eligible patients after the introduction of AAP in the post-ADT, pre-chemotherapy setting	**2,483**	**2,243**	**2,023**	**1,697**	**1,361**

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

The budget impact of current treatment is based on 100% of patients in the post-ADT, pre-chemotherapy setting receiving BSC. In reality, a proportion of the BSC patients may be involved in clinical trials for future therapies, be receiving non-NICE approved drugs funded through the Cancer Drugs Fund or may be not receive active treatment and just be monitored on a regular basis.

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

It is estimated that AA will have a 33% market share in 2014 based on the assumption of AA receiving positive NICE guidance in late Q3 2014. It is estimated that AA would reach a peak of market share of 90% in 2018 (Table 92).

Table 92: Estimated market share of AAP in the post-ADT, pre-chemotherapy setting

	2014	2015	2016	2017	2018
Estimated market share of AAP in the post-ADT setting (%)	33	75	78	80	90

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Cost of treatment and monitoring for AAP were aligned with the median treatment duration in the COU-AA-302 trial and the COU-AA-301 trial. The median durations of treatment were 13.8 months and 8months respectively. Costs of treatment and monitoring associated with the different treatments in the economic model are outlined in section 7.5

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for treatment and monitoring can be found in section 7.5.6.

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

AA also has a licence for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. AAP is currently being used in England and Wales to treat this cohort of patients. With AA's licence extended to the post-ADT, pre-chemotherapy setting, it is anticipated that patients will be treated with AAP earlier in the patient pathway, therefore reducing the use of AAP in the post-chemotherapy setting. It is anticipated that the number of patients eligible for treatment with AAP in the post-chemotherapy setting will decline with the introduction of AAP in the post-ADT, pre-chemotherapy setting.

We have included an estimate of the cost savings as a result of treating fewer patients with AAP in the post-chemotherapy setting. Table 91 provides an estimate of the eligible patients to be treated with AAP in the post-chemotherapy setting depending on whether AAP is available in the post-ADT, pre-chemotherapy setting. If AAP was not available in the post-ADT, pre-chemotherapy setting, the patient pool eligible to receive AAP in the post-chemotherapy setting would be 3,104 patients in 2014 and this figure could rise to 3,189 in 2018. The cost of treating 1,800 patients in 2014 is estimated at £22.2 million and expected to rise to 2,552 patients in 2018 at a cost of £31.5 million.

With the introduction of AAP in the post-ADT, pre-chemotherapy setting, the eligible patient pool for treatment with AAP in the post-chemotherapy setting will decline. In 2014, it is estimated that 1,440 patients would be treated with AAP in the post-chemotherapy setting at a cost of £17.8 million. The number of patients treated with AAP is expected to decline to 1,021 patients in 2018 at a cost of £12.6 million. The cost savings as a result of the reduction of AAP use in the post-ADT, pre-chemotherapy setting is estimated at £4.4 million in 2014 and may increase to £18.9 million in 2018. An overall estimate of the budget impact incorporating these savings has been provided in Table 93.

Table 93: Estimate of the budget impact of AA in the post-chemotherapy setting with and without AA available in the post-ADT, pre-chemotherapy setting

	2014	2015	2016	2017	2018
Without AAP available in the post-ADT setting					
Eligible patient pool	3,104	3,348	3,371	3,394	3,402
AAP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP treatment cost (£[redacted]/month/patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP monitoring cost (£1,737.76 per patient, based on 8 months monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total AAP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With AAP available in the post-ADT setting					
Eligible patient pool	2,483	2,243	2,023	1,697	1,361
AAP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(£[redacted]/month/patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP monitoring cost (£1,737.76 per patient, based on 8 months monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total AAP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost saving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.7 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 Q3 2014, and that AA achieves a market share of 33% in this year, the total budget impact would be £52.2 million in 2014. The maximum budget impact to the NHS could be expected in 2018: £164.4 million. With the PAS, the incremental budget impact would be £22.4 million in 2014 increasing to a maximum budget impact in 2018 of £68.3 million. Table 94 and Table 95 present the estimated budget impact for AA without and with the PAS.

Table 94: Budget impact without PAS

	2014	2015	2016	2017	2018
Estimated eligible patient pool	4,689	4,721	4,754	4,786	4,818
Future treatment of mCRPC patients					
AAP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AA treatment cost (£2,930/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total AAP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost (£20.31/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact (future)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current treatment of mCRPC patients					
PP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost (£20.31/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact (current)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 95: Budget impact with PAS

	2014	2015	2016	2017	2018
Estimated eligible patient pool	4,689	4,721	4,754	4,786	4,818
Future treatment of mCRPC patients					
AAP treatment cost					

Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AA treatment cost (£[redacted]/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total AAP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost					
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost (£20.31/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget Impact (future)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current treatment of mCRPC patients					
PP treatment cost					
Number of patients	4,689	4,721	4,754	4,786	4,818
Market share (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP treatment cost (£20.31/month/pt)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PP cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact (current)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subgroups

Table 96: BPI #3 0–1 Budget impact with PAS

Future treatment budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current treatment budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost saving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 97: ECOG 0 Budget impact with PAS

Future treatment budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current treatment budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost saving	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource sa:vings or redirection of resources that it has not been possible to quantify?

N/A.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

Most recent SPC	SPC annexes	EPAR summary	EPAR full
UK & IE Zytiga 250mg Tablets SmPC Clean 2	Zytiga SPC annexes.pdf	EPAR Zytiga.pdf	EMA WC500137814.pdf

KOL questionnaire

Thinking of your patients that have previously had docetaxel, can you estimate the number of patients that would not be eligible for treatment with abiraterone for each of the following reasons:

Clinician	Patients who die on docetaxel or within 2 months of stopping, %	Patients who are deteriorating too rapidly and would not be suitable AAP, %	Patients with ECOG>2 following docetaxel, %	Patients with uncontrolled hypertension, clinically significant heart disease or cardiac ejection fraction <50%	Total ineligible, %
Dr Chris Parker[a]	<5	5	5–10	<5	15–30
Dr Simon Chowdhury[b]	5–10	10	10	5–10	30–40
Prof Rob Thomas[c]	20	15 together		<5	30–40
Dr Rhona M McMenemin[d]	<5	<5	35	<5	35–45

AAP, abiraterone acetate plus prednisone/prednisolone; ECOG, Eastern Cooperative Oncology Group.

[a]Consultant Clinical Oncologist The Royal Marsden NHS Foundation Trust.

[b]Consultant Medical Oncologist, Guys, King's and St Thomas' Hospital, London.

[c]Consultant Oncologist, Bedford and Addenbrooke's Hospitals.

[d]Consultant Clinical Oncologist, Northern Centre for Cancer Care, Freeman Hospital, Newcastle.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library.**

The literature databases MEDLINE (including MEDLINE In-Process, Other Non-Indexed Citations), Excerpta Medica Database (Embase), and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. MEDLINE and Embase were searched via the Embase.com interface, MEDLINE In-Process and Other Non-Indexed Citations were searched via the PubMed interface, and the CENTRAL was searched via the Cochrane Library's own interface.

10.2.2 The date on which the search was conducted.

The searches were conducted on 02.09.13.

10.2.3 The date span of the search.

The search was limited to material published up to 02.09.13 with no restriction on the search start date.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies used for the searches of the electronic literature databases are shown in the tables below.

It should be noted that the review was conducted in two phases. The original review searched literature from database start to 2010. An update was conducted which included studies published from 2010 until 30.05.11. Searches for 'strontium' and 'zoledronate' were conducted from database start to 1999, in addition to the update search being conducted from 03.10 to 27.09.12. The studies evaluating strontium and zoledronate published between 2000 and 2010 were obtained from the broad review. Another update search was conducted up until 30.05.13, and again until 02.09.13.

10.2.4.1 Embase and MEDLINE search strategies

Table 98: Embase and MEDLINE database search strategy (searched on 30.05.11)

#	Search history
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomized controlled trial' OR 'randomized controlled trial' OR 'randomized controlled trials' OR 'randomized controlled trials'
12	'randomization' OR 'randomization'
13	Rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	'allocated near/2 random'
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'
24	'abstract report'/de
25	'letter'/de
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti
29	#27 OR #28
30	'prostate cancer'/exp
31	'prostate tumor'/de
32	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
33	#30 OR #31 OR #32
34	'fluorouracil'/de
35	fluorouracil:ab,ti OR 'fluoro uracil':ab,ti OR fluouracil:ab,ti OR fu:ab,ti OR adrucil:ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR timazin:ab,ti OR 'ro 2 9757':ab,ti
36	'abiraterone'/de
37	'abiraterone acetate'/de
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti
39	'aflibercept'/de
40	aflibercept:ab,ti OR 'vegf trap':ab,ti
41	as1404:ab,ti OR 'dimethyloxoxanthene acetic acid':ab,ti OR dmxaa:ab,ti OR asa404:ab,ti
42	'atrasentan'/de
43	atrasentan:ab,ti OR xinlay:ab,ti
44	'bevacizumab'/de
45	bevacizumab:ab,ti OR avastin:ab,ti
46	cabazitaxel:ab,ti OR 'taxoid xrp6258':ab,ti OR 'rpr 116258a':ab,ti OR xrp6258:ab,ti
47	'carboplatin'/de
48	carboplatin:ab,ti OR paraplat*:ab,ti OR blastocarb:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR displata:ab,ti OR ercar:ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti OR cbdca:ab,ti OR 'jm 8':ab,ti
49	'cyclophosphamide'/de

#	Search history
50	cyclophosphamid*:ab,ti OR ciclofosfamida:ab,ti OR ciclofosfamide:ab,ti OR claphene:ab,ti OR cp:ab,ti OR cpm:ab,ti OR cyclophospham:ab,ti OR cyclophosphan*:ab,ti OR cytophosphane:ab,ti OR mitoxan:ab,ti OR syklofosfamid:ab,ti OR zytoxan:ab,ti OR clafen:ab,ti OR cytoxan:ab,ti OR neosar:ab,ti OR carloxan:ab,ti OR cicloxal:ab,ti OR cycloblastin*:ab,ti OR 'cyclo cell':ab,ti OR cyclostin:ab,ti OR cyclostine:ab,ti OR cytophosphan:ab,ti OR endoxan*:ab,ti OR enduxan:ab,ti OR fosfaseron:ab,ti OR genoxal:ab,ti OR ledoxina:ab,ti OR procytox:ab,ti OR sendoxan:ab,ti OR ctx:ab,ti OR 'asta b 518':ab,ti OR 'b 518':ab,ti OR 'wr 138719':ab,ti
51	'dasatinib'/de
52	dasatinib:ab,ti OR sprycel:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti
53	'dexamethasone'/de
54	de?amethason*:ab,ti OR dxm:ab,ti OR hexadecadrol:ab,ti OR 'aeroseb dex':ab,ti OR 'alba dex':ab,ti OR decaderm:ab,ti OR decadrol:ab,ti OR decadron:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR 'dex 4':ab,ti OR dexace:ab,ti OR dexameth:ab,ti OR deenar:ab,ti OR deronil:ab,ti OR dezone:ab,ti OR gammacorten:ab,ti OR hexadrol:ab,ti OR maxidex:ab,ti OR aacidexam:ab,ti OR adexone:ab,ti OR aknichthol:ab,ti OR alin:ab,ti OR ambene:ab,ti OR amplidermis:ab,ti OR 'anemul mono':ab,ti OR antimicotico:ab,ti OR aquapred:ab,ti OR auricularum:ab,ti OR auxiloson:ab,ti OR azona:ab,ti OR baycuten:ab,ti OR corson:ab,ti OR cortidexason:ab,ti OR cortisumman:ab,ti OR de?acort:ab,ti OR decalix:ab,ti OR dectancyl:ab,ti OR deltafluorene:ab,ti OR desameton:ab,ti OR dexacortal:ab,ti OR dexacortin:ab,ti OR dexafarma:ab,ti OR dexafluorene:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexamonozon:ab,ti OR dexapos:ab,ti OR dexinoral:ab,ti OR dexone:ab,ti OR dinormon:ab,ti OR fortecortin:ab,ti OR 'lokalison f':ab,ti OR loverine:ab,ti OR millicorten:ab,ti OR mymethasone:ab,ti OR ocasa:ab,ti OR orgadrone:ab,ti OR 'predni f':ab,ti OR spersadex:ab,ti OR visumetazone:ab,ti
55	'docetaxel'/de
56	docetaxel:ab,ti OR taxotere:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti
57	'doxorubicin'/de
58	doxorubicin:ab,ti OR adr:ab,ti OR 'chloridrato de doxorrubicina':ab,ti OR adriamycin:ab,ti OR adriacin:ab,ti OR adriblastin*:ab,ti OR adrimedac:ab,ti OR 'doxo cell':ab,ti OR doxolem:ab,ti OR doxorubin:ab,ti OR farmiblastina:ab,ti OR rubex:ab,ti OR adm:ab,ti OR adria:ab,ti OR dox:ab,ti OR 'fi 106':ab,ti OR doxil:ab,ti OR 'dox sl':ab,ti OR evacet:ab,ti OR lipodox:ab,ti OR caelyx:ab,ti OR doxilen:ab,ti OR 'tlc d 99':ab,ti
59	'estramustine'/de
60	estramustine:ab,ti OR emcyt:ab,ti OR estracyte:ab,ti
61	'etoposide'/de
62	etoposide:ab,ti OR toposar:ab,ti OR vepesid:ab,ti OR lastet:ab,ti OR epeg:ab,ti OR 'vp 16':ab,ti OR 'vp 16 213':ab,ti
63	'hydrocortisone'/de
64	hydrocortisone:ab,ti OR cortifan:ab,ti AND orcortisol:ab,ti OR domolene:ab,ti OR 'barseb hc':ab,ti OR 'komed hc':ab,ti OR 'aeroseb hc':ab,ti OR cetacort:ab,ti OR 'cort dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR eldecort:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR nutracort:ab,ti OR protocort:ab,ti OR rectoid:ab,ti
65	cixutumumab:ab,ti OR 'imc a12':ab,ti
66	'ipilimumab'/de
67	ipilimumab:ab,ti OR 'ctla 4':ab,ti OR ctla4:ab,ti OR 'mdx 010':ab,ti
68	'satraplatin'/de
69	satraplatin:ab,ti OR orplatna:ab,ti OR 'bms 182751':ab,ti OR 'bmy 45594':ab,ti OR jm216:ab,ti
70	'mdv 3100':ab,ti OR mdv3100:ab,ti
71	'mitoxantrone'/de
72	mitoxantrone:ab,ti OR novantrone:ab,ti OR mitozantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mitroxone:ab,ti OR neotalem:ab,ti OR onkotrone:ab,ti OR pralifan:ab,ti OR dhad:ab,ti OR dhaq:ab,ti
73	'paclitaxel'/de
74	paclitaxel:ab,ti OR taxol:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti OR 'taxol konzentrat':ab,ti
75	'epothilone b'/de
76	epothilone:ab,ti OR patupilone:ab,ti OR epo906:ab,ti
77	'prednisolone'/de
78	prednisolone:ab,ti OR metacortandralone:ab,ti OR cortalone:ab,ti OR 'delta cortef':ab,ti OR hydeltra:ab,ti OR hydeltrasol:ab,ti OR 'meti derm':ab,ti OR 'prelone':ab,ti OR adnisolone:ab,ti OR aprednislon:ab,ti OR capsoid:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decaprednil:ab,ti OR deltacortril:ab,ti OR deltasolone:ab,ti OR deltidrosol:ab,ti OR dhasolone:ab,ti OR dontisolon:ab,ti OR estilsona:ab,ti OR fisopred:ab,ti OR frisolona:ab,ti OR gupisone:ab,ti OR hostacortin:ab,ti OR klismacort:ab,ti OR kuhlprednon:ab,ti OR lenisolone:ab,ti OR 'lepi cortinolo':ab,ti OR linola:ab,ti OR longiprednil:ab,ti OR meticortelone:ab,ti OR opredsone:ab,ti OR panafcortelone:ab,ti OR precortisyl:ab,ti OR 'pred clysma':ab,ti OR predeltilone:ab,ti OR 'predni coelin':ab,ti OR prednicortelone:ab,ti OR 'predni helvacort':ab,ti OR prenilone:ab,ti
79	'prednisone'/de
80	prednisone:ab,ti OR deltacortisone:ab,ti OR 'delta cortisone':ab,ti OR deltadehydrocortisone:ab,ti OR metacortandracin:ab,ti OR prednisonum:ab,ti OR deltasone:ab,ti OR 'delta dome':ab,ti OR 'liquid pred':ab,ti OR lisacort:ab,ti OR meticorten:ab,ti OR orasone:ab,ti OR prednicen:ab,ti OR sterapred:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR decortin:ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR deltacortene:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR meprosona:ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR panasol:ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicor*:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti
81	'provenge'/de
82	provenge:ab,ti OR 'sipuleucel t':ab,ti

#	Search history
83	'sunitinib'/de
84	sunitinib:ab,ti OR sutent:ab,ti OR su011248:ab,ti OR su11248:ab,ti
85	'vinblastine'/de
86	vinblastine:ab,ti OR vincaleucoblastine:ab,ti OR velban:ab,ti OR velsar:ab,ti OR vlb:ab,ti
87	'navelbine'/de
88	'vinorelbine ditartrate'/de
89	vinorelbine:ab,ti OR navelbine:ab,ti OR 'anx 530':ab,ti OR biovelbin:ab,ti OR eunades:ab,ti OR nvb:ab,ti OR vnb:ab,ti OR 'kw 2307':ab,ti
90	'zd 4054':ab,ti OR zd4054:ab,ti
91	'strontium'/de
92	strontium:ab,ti OR metastron:ab,ti OR sr89:ab,ti
93	'zoledronic acid'/de
94	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR 'cgp 42446':ab,ti OR cgp42446a:ab,ti OR 'zol 446':ab,ti
95	#91 OR #92 OR #93 OR #94
96	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94
97	#29 AND #33 AND #96
98	#29 AND #33 AND #96 AND [22-3-2010]/sd NOT [31-5-2011]/sd
99	#29 AND #33 AND #95 AND [<1966-1999]/py

Table 99: Embase and MEDLINE database search strategy (searched on 27.02.12)

#	Search History
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'
12	'randomisation' OR 'randomization'
13	rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	'allocated near/2 random'
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'
24	'abstract report'/de
25	'letter'/de
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti
29	#27 OR #28
30	'prostate cancer'/exp
31	'prostate tumor'/de
32	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
33	#30 OR #31 OR #32
34	'fluorouracil'/de

#	Search History
35	fluorouracil:ab,ti OR 'fluoro uracil':ab,ti OR fluouracil:ab,ti OR fu:ab,ti OR adrucil:ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR timazin:ab,ti OR 'ro 2 9757':ab,ti
36	'abiraterone'/de
37	'abiraterone acetate'/de
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti
39	'aflibercept'/de
40	aflibercept:ab,ti OR 'vegf trap':ab,ti
41	as1404:ab,ti OR 'dimethyloxoxanthene acetic acid':ab,ti OR dmxaa:ab,ti OR asa404:ab,ti
42	'atrasentan'/de
43	atrasentan:ab,ti OR xinlay:ab,ti
44	'bevacizumab'/de
45	bevacizumab:ab,ti OR avastin:ab,ti
46	cabazitaxel:ab,ti OR 'taxoid xrp6258':ab,ti OR 'rpr 116258a':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti
47	'carboplatin'/de
48	carboplatin:ab,ti OR paraplat*:ab,ti OR blastocarb:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR displata:ab,ti OR ercar:ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti OR cbdca:ab,ti OR 'jm 8':ab,ti
49	'cyclophosphamide'/de
50	cyclophosphamid*:ab,ti OR ciclofosfamida:ab,ti OR ciclofosfamide:ab,ti OR claphene:ab,ti OR cp:ab,ti OR cpm:ab,ti OR cyclophospham:ab,ti OR cyclophosphan*:ab,ti OR cytophosphane:ab,ti OR mitoxan:ab,ti OR syklofosfamid:ab,ti OR zytoxan:ab,ti OR clafen:ab,ti OR cytoxan:ab,ti OR neosar:ab,ti OR carloxan:ab,ti OR cicloxal:ab,ti OR cycloblastin*:ab,ti OR 'cyclo cell':ab,ti OR cyclostin:ab,ti OR cyclostine:ab,ti OR cytophosphan:ab,ti OR endoxan*:ab,ti OR enduxan:ab,ti OR fosfaseron:ab,ti OR genoxal:ab,ti OR ledoxina:ab,ti OR procytox:ab,ti OR sendoxan:ab,ti OR ctx:ab,ti OR 'asta b 518':ab,ti OR 'b 518':ab,ti OR 'wr 138719':ab,ti
51	'dasatinib'/de
52	dasatinib:ab,ti OR sprycel:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti
53	'dexamethasone'/de
54	de?amethason*:ab,ti OR dxm:ab,ti OR hexadecadrol:ab,ti OR 'aeroseb dex':ab,ti OR 'alba dex':ab,ti OR decaderm:ab,ti OR decadrol:ab,ti OR decadron:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR 'dex 4':ab,ti OR dexace:ab,ti OR dexameth:ab,ti OR deenar:ab,ti OR deronil:ab,ti OR dezone:ab,ti OR gammacorten:ab,ti OR hexadrol:ab,ti OR maxidex:ab,ti OR aacidexam:ab,ti OR adexone:ab,ti OR aknichthol:ab,ti OR alin:ab,ti OR ambene:ab,ti OR amplidermis:ab,ti OR 'anemul mono':ab,ti OR antimicotico:ab,ti OR aquapred:ab,ti OR auricularum:ab,ti OR auxiloson:ab,ti OR azona:ab,ti OR baycuten:ab,ti OR corson:ab,ti OR cortidexason:ab,ti OR cortisumman:ab,ti OR de?acort:ab,ti OR decalix:ab,ti OR dectancyl:ab,ti OR deltafluorene:ab,ti OR desameton:ab,ti OR dexacortal:ab,ti OR dexacortin:ab,ti OR dexafarma:ab,ti OR dexafluorene:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexamonozon:ab,ti OR dexapos:ab,ti OR dexinoral:ab,ti OR dexone:ab,ti OR dinormon:ab,ti OR fortecortin:ab,ti OR 'lokalison f':ab,ti OR loverine:ab,ti OR millicorten:ab,ti OR mymethasone:ab,ti OR ocasa:ab,ti OR orgadrone:ab,ti OR 'predni f':ab,ti OR spersadex:ab,ti OR visumetazone:ab,ti
55	'docetaxel'/de
56	docetaxel:ab,ti OR taxotere:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti
57	'doxorubicin'/de
58	doxorubicin:ab,ti OR adr:ab,ti OR 'chloridrato de doxorrubicina':ab,ti OR adriamycin:ab,ti OR adriacin:ab,ti OR adriblastin*:ab,ti OR adrimedac:ab,ti OR 'doxo cell':ab,ti OR doxolem:ab,ti OR doxorubin:ab,ti OR farmiblastina:ab,ti OR rubex:ab,ti OR adm:ab,ti OR adria:ab,ti OR dox:ab,ti OR 'fi 106':ab,ti OR doxil:ab,ti OR 'dox sl':ab,ti OR evacet:ab,ti OR lipodox:ab,ti OR caelyx:ab,ti OR doxilen:ab,ti OR 'tlc d 99':ab,ti
59	'estramustine'/de
60	estramustine:ab,ti OR emcyt:ab,ti OR estracyt:ab,ti
61	'etoposide'/de
62	etoposide:ab,ti OR toposar:ab,ti OR vepesid:ab,ti OR lastet:ab,ti OR epeg:ab,ti OR 'vp 16':ab,ti OR 'vp 16 213':ab,ti
63	'hydrocortisone'/de
64	hydrocortisone:ab,ti OR cortifan:ab,ti AND orcortisol:ab,ti OR domolene:ab,ti OR 'barseb hc':ab,ti OR 'komed hc':ab,ti OR 'aeroseb hc':ab,ti OR cetacort:ab,ti OR 'cort dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR eldecort:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR nutracort:ab,ti OR protocort:ab,ti OR rectoid:ab,ti
65	cixutumumab:ab,ti OR 'imc a12':ab,ti
66	'ipilimumab'/de
67	ipilimumab:ab,ti OR 'ctla 4':ab,ti OR ctla4:ab,ti OR 'mdx 010':ab,ti
68	'satraplatin'/de
69	satraplatin:ab,ti OR orplatna:ab,ti OR 'bms 182751':ab,ti OR 'bmy 45594':ab,ti OR jm216:ab,ti
70	'mdv 3100':ab,ti OR mdv3100:ab,ti
71	'mitoxantrone'/de
72	mitoxantrone:ab,ti OR novantrone:ab,ti OR mitozantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mitroxone:ab,ti OR neotalem:ab,ti OR onkotrone:ab,ti OR pralifan:ab,ti OR dhad:ab,ti OR dhaq:ab,ti
73	'paclitaxel'/de
74	paclitaxel:ab,ti OR taxol:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti OR 'taxol konzentrat':ab,ti
75	'epothilone b'/de

#	Search History
76	epothilone:ab,ti OR patupilone:ab,ti OR epo906:ab,ti
77	'prednisolone'/de
78	prednisolone:ab,ti OR metacortandralone:ab,ti OR cortalone:ab,ti OR 'delta cortef':ab,ti OR hydeltra:ab,ti OR hydeltrasol:ab,ti OR 'meti derm':ab,ti OR 'prelone':ab,ti OR adnisolone:ab,ti OR aprednislon:ab,ti OR capsoid:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decaprednil:ab,ti OR deltacortril:ab,ti OR deltasolone:ab,ti OR deltidrosol:ab,ti OR dhasolone:ab,ti OR dontisolon:ab,ti OR estilsona:ab,ti OR fisopred:ab,ti OR frisolona:ab,ti OR gupisone:ab,ti OR hostacortin:ab,ti OR klismacort:ab,ti OR kuhlprednon:ab,ti OR lenisolone:ab,ti OR 'lepi cortinolo':ab,ti OR linola:ab,ti OR longiprednil:ab,ti OR meticortelone:ab,ti OR opredsone:ab,ti OR panafcortelone:ab,ti OR precortisyl:ab,ti OR 'pred clysma':ab,ti OR predeltilone:ab,ti OR 'predni coelin':ab,ti OR prednicortelone:ab,ti OR 'predni helvacort':ab,ti OR prenilone:ab,ti
79	'prednisone'/de
80	prednisone:ab,ti OR deltacortisone:ab,ti OR 'delta cortisone':ab,ti OR deltadehydrocortisone:ab,ti OR metacortandracin:ab,ti OR prednisonum:ab,ti OR deltasone:ab,ti OR 'delta dome':ab,ti OR 'liquid pred':ab,ti OR lisacort:ab,ti OR meticorten:ab,ti OR orasone:ab,ti OR prednicen:ab,ti OR sterapred:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR decortin:ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR deltacortene:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR meprosona:ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR panasol:ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicor*:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti
81	'provenge'/de
82	provenge:ab,ti OR 'sipuleucel t':ab,ti
83	'sunitinib'/de
84	sunitinib:ab,ti OR sutent:ab,ti OR su011248:ab,ti OR su11248:ab,ti
85	'vinblastine'/de
86	vinblastine:ab,ti OR vincaleucoblastine:ab,ti OR velban:ab,ti OR velsar:ab,ti OR vlb:ab,ti
87	'navelbine'/de
88	'vinorelbine ditartrate'/de
89	vinorelbine:ab,ti OR navelbine:ab,ti OR 'anx 530':ab,ti OR biovelbin:ab,ti OR eunades:ab,ti OR nvb:ab,ti OR vnb:ab,ti OR 'kw 2307':ab,ti
90	'zd 4054':ab,ti OR zd4054:ab,ti OR zibotentan:ab,ti
91	'strontium'/de
92	strontium:ab,ti OR metastron:ab,ti OR sr89:ab,ti
93	'zoledronic acid'/de
94	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR 'cgp 42446':ab,ti OR cgp42446a:ab,ti OR 'zol 446':ab,ti
95	'zibotentan'/de
96	alpharadin OR 'radium 223' OR 'radium-223'
97	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
98	#29 AND #33 AND #97
99	#29 AND #33 AND #97 AND [31-05-2011]/sd
100	#29 AND #33 AND #96
101	#99 OR #100

Table 100: Embase and MEDLINE database search strategy (searched on 27.09.12)

#	Search History
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'
12	'randomisation' OR 'randomization'
13	rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	allocated NEAR/2 random

18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'
24	'abstract report'/de
25	'letter'/de
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti
29	#27 OR #28
30	'prostate cancer'/exp
31	'prostate tumor'/de
32	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
33	#30 OR #31 OR #32
34	'fluorouracil'/de
35	fluorouracil:ab,ti OR 'fluoro uracil':ab,ti OR fluouracil:ab,ti OR fu:ab,ti OR adrucil:ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR timazin:ab,ti OR 'ro 2 9757':ab,ti
36	'abiraterone'/de
37	'abiraterone acetate'/de
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti
39	'aflibercept'/de
40	aflibercept:ab,ti OR 'vegf trap':ab,ti
41	as1404:ab,ti OR 'dimethyloxoxanthene acetic acid':ab,ti OR dmxaa:ab,ti OR asa404:ab,ti
42	'atrasentan'/de
43	atrasentan:ab,ti OR xinlay:ab,ti
44	'bevacizumab'/de
45	bevacizumab:ab,ti OR avastin:ab,ti
46	cabazitaxel:ab,ti OR 'taxoid xrp6258':ab,ti OR 'rpr 116258a':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti
47	'cabazitaxel'/de
48	'carboplatin'/de
49	carboplatin:ab,ti OR paraplat*:ab,ti OR blastocarb:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR displata:ab,ti OR ercar:ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti OR cbdca:ab,ti OR 'jm 8':ab,ti
50	'cyclophosphamide'/de
51	cyclophosphamid*:ab,ti OR ciclofosfamida:ab,ti OR ciclofosfamide:ab,ti OR claphene:ab,ti OR cp:ab,ti OR cpm:ab,ti OR cyclophospham:ab,ti OR cyclophosphan*:ab,ti OR cytophosphane:ab,ti OR mitoxan:ab,ti OR syklofosfamid:ab,ti OR zytoxan:ab,ti OR clafen:ab,ti OR cytoxan:ab,ti OR neosar:ab,ti OR carloxan:ab,ti OR cicloxal:ab,ti OR cycloblastin*:ab,ti OR 'cyclo cell':ab,ti OR cyclostin:ab,ti OR cyclostine:ab,ti OR cytophosphan:ab,ti OR endoxan*:ab,ti OR enduxan:ab,ti OR fosfaseron:ab,ti OR genoxal:ab,ti OR ledoxina:ab,ti OR procytox:ab,ti OR sendoxan:ab,ti OR ctx:ab,ti OR 'asta b 518':ab,ti OR 'b 518':ab,ti OR 'wr 138719':ab,ti
52	'dasatinib'/de
53	dasatinib:ab,ti OR sprycel:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti
54	'dexamethasone'/de
55	de?amethason*:ab,ti OR dxm:ab,ti OR hexadecadrol:ab,ti OR 'aeroseb dex':ab,ti OR 'alba dex':ab,ti OR decaderm:ab,ti OR decadrol:ab,ti OR decadron:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR 'dex 4':ab,ti OR dexace:ab,ti OR dexameth:ab,ti OR deenar:ab,ti OR deronil:ab,ti OR dezone:ab,ti OR gammacorten:ab,ti OR hexadrol:ab,ti OR maxidex:ab,ti OR aacidexam:ab,ti OR adexone:ab,ti OR aknichthol:ab,ti OR alin:ab,ti OR ambene:ab,ti OR amplidermis:ab,ti OR 'anemul mono':ab,ti OR antimicotico:ab,ti OR aquapred:ab,ti OR auricularum:ab,ti OR auxiloson:ab,ti OR azona:ab,ti OR baycuten:ab,ti OR corson:ab,ti OR cortidexason:ab,ti OR cortisumman:ab,ti OR de?acort:ab,ti OR decalix:ab,ti OR dectancyl:ab,ti OR deltafluorene:ab,ti OR desameton:ab,ti OR dexacortal:ab,ti OR dexacortin:ab,ti OR dexafarma:ab,ti OR dexafluorene:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexamonozon:ab,ti OR dexapos:ab,ti OR dexinoral:ab,ti OR dexone:ab,ti OR dinormon:ab,ti OR fortecortin:ab,ti OR 'lokalison f':ab,ti OR loverine:ab,ti OR millicorten:ab,ti OR mymethasone:ab,ti OR ocasa:ab,ti OR orgadrone:ab,ti OR 'predni f':ab,ti OR spersadex:ab,ti OR visumetazone:ab,ti
56	'docetaxel'/de
57	docetaxel:ab,ti OR taxotere:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti
58	'doxorubicin'/de
59	doxorubicin:ab,ti OR adr:ab,ti OR 'chloridrato de doxorrubicina':ab,ti OR adriamycin:ab,ti OR adriacin:ab,ti OR adriblastin*:ab,ti OR adrimedac:ab,ti OR 'doxo cell':ab,ti OR doxolem:ab,ti OR doxorubin:ab,ti OR farmiblastina:ab,ti OR rubex:ab,ti OR adm:ab,ti OR adria:ab,ti OR dox:ab,ti OR 'fi 106':ab,ti OR doxil:ab,ti OR 'dox sl':ab,ti OR evacet:ab,ti OR lipodox:ab,ti OR caelyx:ab,ti OR doxilen:ab,ti OR 'tlc d 99':ab,ti
60	'estramustine'/de

61	estramustine:ab,ti OR emcyt:ab,ti OR estracyt:ab,ti
62	'etoposide'/de
63	etoposide:ab,ti OR toposar:ab,ti OR vepesid:ab,ti OR lastet:ab,ti OR epeg:ab,ti OR 'vp 16':ab,ti OR 'vp 16 213':ab,ti
64	'hydrocortisone'/de
65	hydrocortisone:ab,ti OR cortifan:ab,ti OR orcortisol:ab,ti OR domolene:ab,ti OR 'barseb hc':ab,ti OR 'komed hc':ab,ti OR 'aeroseb hc':ab,ti OR cetacort:ab,ti OR 'cort dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR eldecort:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR nutracort:ab,ti OR protocort:ab,ti OR rectoid:ab,ti
66	cixutumumab:ab,ti OR 'imc a12':ab,ti
67	'ipilimumab'/de
68	ipilimumab:ab,ti OR 'ctla 4':ab,ti OR ctla4:ab,ti OR 'mdx 010':ab,ti
69	'satraplatin'/de
70	satraplatin:ab,ti OR orplatna:ab,ti OR 'bms 182751':ab,ti OR 'bmy 45594':ab,ti OR jm216:ab,ti
71	'mdv 3100':ab,ti OR mdv3100:ab,ti or enzalutamide:ab,ti OR xtandi:ab,ti
72	'4 [3 [4 cyano 3 (trifluoromethyl) phenyl] 5, 5 dimethyl 4 oxo 2 thioxo 1 imidazolidinyl] 2 fluoro n methylbenzamide'/de
73	'mitoxantrone'/de
74	mitoxantrone:ab,ti OR novantrone:ab,ti OR mitozantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mitroxone:ab,ti OR neotalem:ab,ti OR onkotrone:ab,ti OR pralifan:ab,ti OR dhad:ab,ti OR dhaq:ab,ti
75	'paclitaxel'/de
76	paclitaxel:ab,ti OR taxol:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti OR 'taxol konzentrat':ab,ti
77	'epothilone b'/de
78	epothilone:ab,ti OR patupilone:ab,ti OR epo906:ab,ti
79	'prednisolone'/de
80	prednisolone:ab,ti OR metacortandralone:ab,ti OR cortalone:ab,ti OR 'delta cortef':ab,ti OR hydeltra:ab,ti OR hydeltrasol:ab,ti OR 'meti derm':ab,ti OR 'prelone':ab,ti OR adnisolone:ab,ti OR aprednislon:ab,ti OR capsoid:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decaprednil:ab,ti OR deltacortril:ab,ti OR deltasolone:ab,ti OR deltidrosol:ab,ti OR dhasolone:ab,ti OR dontisolon:ab,ti OR estilsona:ab,ti OR fisopred:ab,ti OR frisolona:ab,ti OR gupisone:ab,ti OR hostacortin:ab,ti OR klismacort:ab,ti OR kuhlprednon:ab,ti OR lenisolone:ab,ti OR 'lepi cortinolo':ab,ti OR linola:ab,ti OR longiprednil:ab,ti OR meticortelone:ab,ti OR opredsone:ab,ti OR panafcortelone:ab,ti OR precortisyl:ab,ti OR 'pred clysma':ab,ti OR predeltilone:ab,ti OR 'predni coelin':ab,ti OR prednicortelone:ab,ti OR 'predni helvacort':ab,ti OR prenilone:ab,ti
81	'prednisone'/de
82	prednisone:ab,ti OR deltacortisone:ab,ti OR 'delta cortisone':ab,ti OR deltadehydrocortisone:ab,ti OR metacortandracin:ab,ti OR prednisonum:ab,ti OR deltasone:ab,ti OR 'delta dome':ab,ti OR 'liquid pred':ab,ti OR lisacort:ab,ti OR meticorten:ab,ti OR orasone:ab,ti OR prednicen:ab,ti OR sterapred:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR decortin:ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR deltacortene:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR meprosona:ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR panasol:ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicor*:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti
83	'provenge'/de
84	provenge:ab,ti OR 'sipuleucel t':ab,ti
85	'sunitinib'/de
86	sunitinib:ab,ti OR sutent:ab,ti OR su011248:ab,ti OR su11248:ab,ti
87	'vinblastine'/de
88	vinblastine:ab,ti OR vincaleucoblastine:ab,ti OR velban:ab,ti OR velsar:ab,ti OR vlb:ab,ti
89	'navelbine'/de
90	'vinorelbine ditartrate'/de
91	vinorelbine:ab,ti OR navelbine:ab,ti OR 'anx 530':ab,ti OR biovelbin:ab,ti OR eunades:ab,ti OR nvb:ab,ti OR vnb:ab,ti OR 'kw 2307':ab,ti
92	'zd 4054':ab,ti OR zd4054:ab,ti OR zibotentan:ab,ti
93	'strontium'/de
94	strontium:ab,ti OR metastron:ab,ti OR sr89:ab,ti
95	'zoledronic acid'/de
96	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR 'cgp 42446':ab,ti OR cgp42446a:ab,ti OR 'zol 446':ab,ti
97	'zibotentan'/de
98	alpharadin OR 'radium 223' OR 'radium-223'
99	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
100	#29 AND #33 AND #99
101	#29 AND #33 AND #99 AND [27-09-2012]/sd

Table 101: Embase and MEDLINE database search strategy (searched on 30.05.13)

#	Search History
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'
12	'randomisation' OR 'randomization'
13	rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	allocated NEAR/2 random
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'
24	'abstract report'/de
25	'letter'/de
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti
29	#27 OR #28
30	'prostate cancer'/exp
31	'prostate tumor'/de
32	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
33	#30 OR #31 OR #32
34	'fluorouracil'/de
35	fluorouracil:ab,ti OR 'fluoro uracil':ab,ti OR fluouracil:ab,ti OR fu:ab,ti OR adrucil:ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR timazin:ab,ti OR 'ro 2 9757':ab,ti
36	'abiraterone'/de
37	'abiraterone acetate'/de
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti
39	'aflibercept'/de
40	aflibercept:ab,ti OR 'vegf trap':ab,ti
41	as1404:ab,ti OR 'dimethyloxoxanthene acetic acid':ab,ti OR dmxaa:ab,ti OR asa404:ab,ti
42	'atrasentan'/de
43	atrasentan:ab,ti OR xinlay:ab,ti
44	'bevacizumab'/de
45	bevacizumab:ab,ti OR avastin:ab,ti
46	cabazitaxel:ab,ti OR 'taxoid xrp6258':ab,ti OR 'rpr 116258a':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti
47	'cabazitaxel'/de
48	'carboplatin'/de
49	carboplatin:ab,ti OR paraplat*:ab,ti OR blastocarb:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR displata:ab,ti OR ercar:ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti OR cbdca:ab,ti OR 'jm 8':ab,ti
50	'cyclophosphamide'/de
51	cyclophosphamid*:ab,ti OR ciclofosfamida:ab,ti OR ciclofosfamide:ab,ti OR claphene:ab,ti OR cp:ab,ti OR cpm:ab,ti OR cyclophospham:ab,ti OR cyclophosphan*:ab,ti OR cytophosphane:ab,ti OR mitoxan:ab,ti OR syklofosfamid:ab,ti OR zytoxan:ab,ti OR clafen:ab,ti OR cytoxan:ab,ti OR neosar:ab,ti OR carloxan:ab,ti OR cicloxal:ab,ti OR cycloblastin*:ab,ti OR 'cyclo cell':ab,ti OR cyclostin:ab,ti OR cyclostine:ab,ti OR cytophosphan:ab,ti OR endoxan*:ab,ti OR enduxan:ab,ti OR fosfaseron:ab,ti OR genoxal:ab,ti OR ledoxina:ab,ti OR procytox:ab,ti OR sendoxan:ab,ti OR ctx:ab,ti OR 'asta b 518':ab,ti OR 'b 518':ab,ti OR 'wr 138719':ab,ti

52	'dasatinib'/de
53	dasatinib:ab,ti OR sprycel:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti
54	'dexamethasone'/de
55	de?amethason*:ab,ti OR dxm:ab,ti OR hexadecadrol:ab,ti OR 'aeroseb dex':ab,ti OR 'alba dex':ab,ti OR decaderm:ab,ti OR decadrol:ab,ti OR decadron:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR 'dex 4':ab,ti OR dexace:ab,ti OR dexameth:ab,ti OR deenar:ab,ti OR deronil:ab,ti OR dezone:ab,ti OR gammacorten:ab,ti OR hexadrol:ab,ti OR maxidex:ab,ti OR aacidexam:ab,ti OR adexone:ab,ti OR aknichthol:ab,ti OR alin:ab,ti OR ambene:ab,ti OR amplidermis:ab,ti OR 'anemul mono':ab,ti OR antimicotico:ab,ti OR aquapred:ab,ti OR auricularum:ab,ti OR auxiloson:ab,ti OR azona:ab,ti OR baycuten:ab,ti OR corson:ab,ti OR cortidexason:ab,ti OR cortisumman:ab,ti OR de?acort:ab,ti OR decalix:ab,ti OR dectancyl:ab,ti OR deltafluorene:ab,ti OR desameton:ab,ti OR dexacortal:ab,ti OR dexacortin:ab,ti OR dexafarma:ab,ti OR dexafluorene:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexamonozon:ab,ti OR dexapos:ab,ti OR dexinoral:ab,ti OR dexone:ab,ti OR dinormon:ab,ti OR fortecortin:ab,ti OR 'lokalison f':ab,ti OR loverine:ab,ti OR millicorten:ab,ti OR mymethasone:ab,ti OR ocasa:ab,ti OR orgadrone:ab,ti OR 'predni f':ab,ti OR spersadex:ab,ti OR visumetazone:ab,ti
56	'docetaxel'/de
57	docetaxel:ab,ti OR taxotere:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti
58	'doxorubicin'/de
59	doxorubicin:ab,ti OR adr:ab,ti OR 'chloridrato de doxorrubicina':ab,ti OR adriamycin:ab,ti OR adriacin:ab,ti OR adriblastin*:ab,ti OR adrimedac:ab,ti OR 'doxo cell':ab,ti OR doxolem:ab,ti OR doxorubin:ab,ti OR farmiblastina:ab,ti OR rubex:ab,ti OR adm:ab,ti OR adria:ab,ti OR dox:ab,ti OR 'fi 106':ab,ti OR doxil:ab,ti OR 'dox sl':ab,ti OR evacet:ab,ti OR lipodox:ab,ti OR caelyx:ab,ti OR doxilen:ab,ti OR 'tlc d 99':ab,ti
60	'estramustine'/de
61	estramustine:ab,ti OR emcyt:ab,ti OR estracyt:ab,ti
62	'etoposide'/de
63	etoposide:ab,ti OR toposar:ab,ti OR vepesid:ab,ti OR lastet:ab,ti OR epeg:ab,ti OR 'vp 16':ab,ti OR 'vp 16 213':ab,ti
64	'hydrocortisone'/de
65	hydrocortisone:ab,ti OR cortifan:ab,ti OR orcortisol:ab,ti OR domolene:ab,ti OR 'barseb hc':ab,ti OR 'komed hc':ab,ti OR 'aeroseb hc':ab,ti OR cetacort:ab,ti OR 'cort dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR eldecort:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR nutracort:ab,ti OR protocort:ab,ti OR rectoid:ab,ti
66	cixutumumab:ab,ti OR 'imc a12':ab,ti
67	'ipilimumab'/de
68	ipilimumab:ab,ti OR 'ctla 4':ab,ti OR ctla4:ab,ti OR 'mdx 010':ab,ti
69	'satraplatin'/de
70	satraplatin:ab,ti OR orplatna:ab,ti OR 'bms 182751':ab,ti OR 'bmy 45594':ab,ti OR jm216:ab,ti
71	'mdv 3100':ab,ti OR mdv3100:ab,ti or enzalutamide:ab,ti OR xtandi:ab,ti
72	'4 [3 [4 cyano 3 (trifluoromethyl) phenyl] 5, 5 dimethyl 4 oxo 2 thioxo 1 imidazolidinyl] 2 fluoro n methylbenzamide'/de
73	'mitoxantrone'/de
74	mitoxantrone:ab,ti OR novantrone:ab,ti OR mitozantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mitroxone:ab,ti OR neotalem:ab,ti OR onkotrone:ab,ti OR pralifan:ab,ti OR dhad:ab,ti OR dhaq:ab,ti
75	'paclitaxel'/de
76	paclitaxel:ab,ti OR taxol:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti OR 'taxol konzentrat':ab,ti
77	'epothilone b'/de
78	epothilone:ab,ti OR patupilone:ab,ti OR epo906:ab,ti
79	'prednisolone'/de
80	prednisolone:ab,ti OR metacortandralone:ab,ti OR cortalone:ab,ti OR 'delta cortef':ab,ti OR hydeltra:ab,ti OR hydeltrasol:ab,ti OR 'meti derm':ab,ti OR 'prelone':ab,ti OR adnisolone:ab,ti OR aprednislon:ab,ti OR capsoid:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decaprednil:ab,ti OR deltacortril:ab,ti OR deltasolone:ab,ti OR deltidrosol:ab,ti OR dhasolone:ab,ti OR dontisolon:ab,ti OR estilsona:ab,ti OR fisopred:ab,ti OR frisolona:ab,ti OR gupisone:ab,ti OR hostacortin:ab,ti OR klismacort:ab,ti OR kuhlprednon:ab,ti OR lenisolone:ab,ti OR 'lepi cortinolo':ab,ti OR linola:ab,ti OR longiprednil:ab,ti OR meticortelone:ab,ti OR opredsone:ab,ti OR panafcortelone:ab,ti OR precortisyl:ab,ti OR 'pred clysma':ab,ti OR predeltilone:ab,ti OR 'predni coelin':ab,ti OR prednicortelone:ab,ti OR 'predni helvacort':ab,ti OR prenilone:ab,ti
81	'prednisone'/de
82	prednisone:ab,ti OR deltacortisone:ab,ti OR 'delta cortisone':ab,ti OR deltadehydrocortisone:ab,ti OR metacortandracin:ab,ti OR prednisonum:ab,ti OR deltasone:ab,ti OR 'delta dome':ab,ti OR 'liquid pred':ab,ti OR lisacort:ab,ti OR meticorten:ab,ti OR orasone:ab,ti OR prednicen:ab,ti OR sterapred:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR decortin:ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR deltacortene:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR meprosona:ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR panasol:ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicor*:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti
83	'provenge'/de
84	provenge:ab,ti OR 'sipuleucel t':ab,ti
85	'sunitinib'/de
86	sunitinib:ab,ti OR sutent:ab,ti OR su011248:ab,ti OR su11248:ab,ti
87	'vinblastine'/de
88	vinblastine:ab,ti OR vincaleucoblastine:ab,ti OR velban:ab,ti OR velsar:ab,ti OR vlb:ab,ti

89	'navelbine'/de
90	'vinorelbine ditartrate'/de
91	vinorelbine:ab,ti OR navelbine:ab,ti OR 'anx 530':ab,ti OR biovelbin:ab,ti OR eunades:ab,ti OR nvb:ab,ti OR vnb:ab,ti OR 'kw 2307':ab,ti
92	'zd 4054':ab,ti OR zd4054:ab,ti OR zibotentan:ab,ti
93	'strontium'/de
94	strontium:ab,ti OR metastron:ab,ti OR sr89:ab,ti
95	'zoledronic acid'/de
96	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR 'cgp 42446':ab,ti OR cgp42446a:ab,ti OR 'zol 446':ab,ti
97	'zibotentan'/de
98	alpharadin OR 'radium 223' OR 'radium-223'
99	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
100	#29 AND #33 AND #99
101	**#100** AND [27-9-2012]/sd

Table 102: Embase and MEDLINE database search strategy (searched on 02.09.13)

#	Search History
1	'clinical trial'/exp
2	'randomization'/de
3	'controlled study'/de
4	'comparative study'/de
5	'single blind procedure'/de
6	'double blind procedure'/de
7	'crossover procedure'/de
8	'placebo'/de
9	'clinical trial' OR 'clinical trials'
10	'controlled clinical trial' OR 'controlled clinical trials'
11	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'
12	'randomisation' OR 'randomization'
13	rct
14	'random allocation'
15	'randomly allocated'
16	'allocated randomly'
17	allocated NEAR/2 random
18	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)
19	placebo*
20	'prospective study'/de
21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22	'case study'/de
23	'case report'
24	'abstract report'/de
25	'letter'/de
26	#22 OR #23 OR #24 OR #25
27	#21 NOT #26
28	'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'clinical article'/exp OR 'intervention study'/exp OR 'survival'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR (clinical NEXT/1 trial*):ab,ti OR 'retrospective study'/exp OR 'case control study'/exp OR (case* NEXT/1 control*):ab,ti
29	#27 OR #28
30	'prostate cancer'/exp
31	'prostate tumor'/de
32	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
33	#30 OR #31 OR #32
34	'fluorouracil'/de
35	fluorouracil:ab,ti OR 'fluoro uracil':ab,ti OR fluouracil:ab,ti OR fu:ab,ti OR adrucil:ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR timazin:ab,ti OR 'ro 2 9757':ab,ti
36	'abiraterone'/de
37	'abiraterone acetate'/de
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti

39	'aflibercept'/de
40	aflibercept:ab,ti OR 'vegf trap':ab,ti
41	as1404:ab,ti OR 'dimethyloxoxanthene acetic acid':ab,ti OR dmxaa:ab,ti OR asa404:ab,ti
42	'atrasentan'/de
43	atrasentan:ab,ti OR xinlay:ab,ti
44	'bevacizumab'/de
45	bevacizumab:ab,ti OR avastin:ab,ti
46	cabazitaxel:ab,ti OR 'taxoid xrp6258':ab,ti OR 'rpr 116258a':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti
47	'cabazitaxel'/de
48	'carboplatin'/de
49	carboplatin:ab,ti OR paraplat*:ab,ti OR blastocarb:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR displata:ab,ti OR ercar:ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti OR cbdca:ab,ti OR 'jm 8':ab,ti
50	'cyclophosphamide'/de
51	cyclophosphamid*:ab,ti OR ciclofosfamida:ab,ti OR ciclofosfamide:ab,ti OR claphene:ab,ti OR cp:ab,ti OR cpm:ab,ti OR cyclophospham:ab,ti OR cyclophosphan*:ab,ti OR cytophosphane:ab,ti OR mitoxan:ab,ti OR syklofosfamid:ab,ti OR zytoxan:ab,ti OR clafen:ab,ti OR cytoxan:ab,ti OR neosar:ab,ti OR carloxan:ab,ti OR cicloxal:ab,ti OR cycloblastin*:ab,ti OR 'cyclo cell':ab,ti OR cyclostin:ab,ti OR cyclostine:ab,ti OR cytophosphan:ab,ti OR endoxan*:ab,ti OR enduxan:ab,ti OR fosfaseron:ab,ti OR genoxal:ab,ti OR ledoxina:ab,ti OR procytox:ab,ti OR sendoxan:ab,ti OR ctx:ab,ti OR 'asta b 518':ab,ti OR 'b 518':ab,ti OR 'wr 138719':ab,ti
52	'dasatinib'/de
53	dasatinib:ab,ti OR sprycel:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti
54	'dexamethasone'/de
55	de?amethason*:ab,ti OR dxm:ab,ti OR hexadecadrol:ab,ti OR 'aeroseb dex':ab,ti OR 'alba dex':ab,ti OR decaderm:ab,ti OR decadrol:ab,ti OR decadron:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR 'dex 4':ab,ti OR dexace:ab,ti OR dexameth:ab,ti OR deenar:ab,ti OR deronil:ab,ti OR dezone:ab,ti OR gammacorten:ab,ti OR hexadrol:ab,ti OR maxidex:ab,ti OR aacidexam:ab,ti OR adexone:ab,ti OR aknichthol:ab,ti OR alin:ab,ti OR ambene:ab,ti OR amplidermis:ab,ti OR 'anemul mono':ab,ti OR antimicotico:ab,ti OR aquapred:ab,ti OR auricularum:ab,ti OR auxiloson:ab,ti OR azona:ab,ti OR baycuten:ab,ti OR corson:ab,ti OR cortidexason:ab,ti OR cortisumman:ab,ti OR de?acort:ab,ti OR decalix:ab,ti OR dectancyl:ab,ti OR deltafluorene:ab,ti OR desameton:ab,ti OR dexacortal:ab,ti OR dexacortin:ab,ti OR dexafarma:ab,ti OR dexafluorene:ab,ti OR dexalocal:ab,ti OR dexamecortin:ab,ti OR dexamonozon:ab,ti OR dexapos:ab,ti OR dexinoral:ab,ti OR dexone:ab,ti OR dinormon:ab,ti OR fortecortin:ab,ti OR 'lokalison f':ab,ti OR loverine:ab,ti OR millicorten:ab,ti OR mymethasone:ab,ti OR ocasa:ab,ti OR orgadrone:ab,ti OR 'predni f':ab,ti OR spersadex:ab,ti OR visumetazone:ab,ti
56	'docetaxel'/de
57	docetaxel:ab,ti OR taxotere:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti
58	'doxorubicin'/de
59	doxorubicin:ab,ti OR adr:ab,ti OR 'chloridrato de doxorrubicina':ab,ti OR adriamycin:ab,ti OR adriacin:ab,ti OR adriblastin*:ab,ti OR adrimedac:ab,ti OR 'doxo cell':ab,ti OR doxolem:ab,ti OR doxorubin:ab,ti OR farmiblastina:ab,ti OR rubex:ab,ti OR adm:ab,ti OR adria:ab,ti OR dox:ab,ti OR 'fi 106':ab,ti OR doxil:ab,ti OR 'dox sl':ab,ti OR evacet:ab,ti OR lipodox:ab,ti OR caelyx:ab,ti OR doxilen:ab,ti OR 'tlc d 99':ab,ti
60	'estramustine'/de
61	estramustine:ab,ti OR emcyt:ab,ti OR estracyt:ab,ti
62	'etoposide'/de
63	etoposide:ab,ti OR toposar:ab,ti OR vepesid:ab,ti OR lastet:ab,ti OR epeg:ab,ti OR 'vp 16':ab,ti OR 'vp 16 213':ab,ti
64	'hydrocortisone'/de
65	hydrocortisone:ab,ti OR cortifan:ab,ti OR orcortisol:ab,ti OR domolene:ab,ti OR 'barseb hc':ab,ti OR 'komed hc':ab,ti OR 'aeroseb hc':ab,ti OR cetacort:ab,ti OR 'cort dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR eldecort:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR nutracort:ab,ti OR protocort:ab,ti OR rectoid:ab,ti
66	cixutumumab:ab,ti OR 'imc a12':ab,ti
67	'ipilimumab'/de
68	ipilimumab:ab,ti OR 'ctla 4':ab,ti OR ctla4:ab,ti OR 'mdx 010':ab,ti
69	'satraplatin'/de
70	satraplatin:ab,ti OR orplatna:ab,ti OR 'bms 182751':ab,ti OR 'bmy 45594':ab,ti OR jm216:ab,ti
71	'mdv 3100':ab,ti OR mdv3100:ab,ti or enzalutamide:ab,ti OR xtandi:ab,ti
72	'4 [3 [4 cyano 3 (trifluoromethyl) phenyl] 5, 5 dimethyl 4 oxo 2 thioxo 1 imidazolidinyl] 2 fluoro n methylbenzamide'/de
73	'mitoxantrone'/de
74	mitoxantrone:ab,ti OR novantrone:ab,ti OR mitozantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mitroxone:ab,ti OR neotalem:ab,ti OR onkotrone:ab,ti OR pralifan:ab,ti OR dhad:ab,ti OR dhaq:ab,ti
75	'paclitaxel'/de
76	paclitaxel:ab,ti OR taxol:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti OR 'taxol konzentrat':ab,ti
77	'epothilone b'/de
78	epothilone:ab,ti OR patupilone:ab,ti OR epo906:ab,ti
79	'prednisolone'/de

80	prednisolone:ab,ti OR metacortandralone:ab,ti OR cortalone:ab,ti OR 'delta cortef':ab,ti OR hydeltra:ab,ti OR hydeltrasol:ab,ti OR 'meti derm':ab,ti OR 'prelone':ab,ti OR adnisolone:ab,ti OR aprednislon:ab,ti OR capsoid:ab,ti OR cortisolone:ab,ti OR dacortin:ab,ti OR decaprednil:ab,ti OR deltacortril:ab,ti OR deltasolone:ab,ti OR deltidrosol:ab,ti OR dhasolone:ab,ti OR dontisolon:ab,ti OR estilsona:ab,ti OR fisopred:ab,ti OR frisolona:ab,ti OR gupisone:ab,ti OR hostacortin:ab,ti OR klismacort:ab,ti OR kuhlprednon:ab,ti OR lenisolone:ab,ti OR 'lepi cortinolo':ab,ti OR linola:ab,ti OR longiprednil:ab,ti OR meticortelone:ab,ti OR opredsone:ab,ti OR panafcortelone:ab,ti OR precortisyl:ab,ti OR 'pred clysma':ab,ti OR predeltilone:ab,ti OR 'predni coelin':ab,ti OR prednicortelone:ab,ti OR 'predni helvacort':ab,ti OR prenilone:ab,ti
81	'prednisone'/de
82	prednisone:ab,ti OR deltacortisone:ab,ti OR 'delta cortisone':ab,ti OR deltadehydrocortisone:ab,ti OR metacortandracin:ab,ti OR prednisonum:ab,ti OR deltasone:ab,ti OR 'delta dome':ab,ti OR 'liquid pred':ab,ti OR lisacort:ab,ti OR meticorten:ab,ti OR orasone:ab,ti OR prednicen:ab,ti OR sterapred:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR decortin:ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR deltacortene:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR meprosona:ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR panasol:ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicor*:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti
83	'provenge'/de
84	provenge:ab,ti OR 'sipuleucel t':ab,ti
85	'sunitinib'/de
86	sunitinib:ab,ti OR sutent:ab,ti OR su011248:ab,ti OR su11248:ab,ti
87	'vinblastine'/de
88	vinblastine:ab,ti OR vincaleucoblastine:ab,ti OR velban:ab,ti OR velsar:ab,ti OR vlb:ab,ti
89	'navelbine'/de
90	'vinorelbine ditartrate'/de
91	vinorelbine:ab,ti OR navelbine:ab,ti OR 'anx 530':ab,ti OR biovelbin:ab,ti OR eunades:ab,ti OR nvb:ab,ti OR vnb:ab,ti OR 'kw 2307':ab,ti
92	'zd 4054':ab,ti OR zd4054:ab,ti OR zibotentan:ab,ti
93	'strontium'/de
94	strontium:ab,ti OR metastron:ab,ti OR sr89:ab,ti
95	'zoledronic acid'/de
96	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR 'cgp 42446':ab,ti OR cgp42446a:ab,ti OR 'zol 446':ab,ti
97	'zibotentan'/de
98	alpharadin OR 'radium 223' OR 'radium-223'
99	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
100	#29 AND #33 AND #99
101	**#100 AND [31-5-2013]/sd**

10.2.4.2 Cochrane (CENTRAL) search strategies

Table 103: Cochrane (CENTRAL) database search strategy (searched on 30the May 2011)

#	Search History
1	MeSH descriptor Prostatic Neoplasms, this term only
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
3	(#1 OR #2)
4	MeSH descriptor Fluorouracil, this term only
5	fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flurablastin OR fluracedyl OR fluracil OR fluril OR fluroblastin OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
6	abiraterone OR 'cb 7598' OR cb7598 OR 'abiraterone acetate' OR zytiga
7	aflibercept OR 'vegf trap'
8	as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
9	atrasentan OR xinlay
10	bevacizumab OR avastin
11	cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
12	MeSH descriptor Carboplatin, this term only
13	carboplatin OR paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
14	MeSH descriptor Cyclophosphamide, this term only

#	Search History
15	cyclophosphamid* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophospham OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
16	dasatinib OR sprycel OR 'bms 354825' OR bms354825
17	MeSH descriptor Dexamethasone, this term only
18	de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	docetaxel OR taxotere OR 'rp 56976' OR rp56976
20	MeSH descriptor Doxorubicin, this term only
21	doxorubicin OR adr OR 'chloridrato de doxorrubicina' OR adriamycin OR adriacin OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
22	estramustine OR emcyt OR estracyte
23	MeSH descriptor Etoposide, this term only
24	etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
25	MeSH descriptor Hydrocortisone, this term only
26	hydrocortisone OR cortifan AND orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
27	cixutumumab OR 'imc a12'
28	ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010'
29	satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
30	'mdv 3100' OR mdv3100
31	MeSH descriptor Mitoxantrone, this term only
32	mitoxantrone OR novantrone OR mitozantrone OR dihydroxyanthracenedione OR mitroxone OR neotalem OR onkotrone OR pralifan OR dhad OR dhaq
33	MeSH descriptor Paclitaxel, this term only
34	paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
35	MeSH descriptor Epothilones, this term only
36	epothilone OR patupilone OR epo906
37	MeSH descriptor Prednisolone, this term only
38	prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
39	MeSH descriptor Prednisone, this term only
40	prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
41	provenge OR 'sipuleucel t'
42	sunitinib OR sutent OR su011248 OR su11248
43	MeSH descriptor Vinblastine, this term only
44	vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
45	vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
46	'zd 4054' OR zd4054
47	MeSH descriptor Strontium, this term only
48	strontium OR metastron OR sr89
49	'zoledronic acid' OR zoledronate OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
50	(#47 OR #48 OR #49)
51	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49)
52	(#3 AND #50), Limited to 1900 to 1999, in CENTRAL database
53	(#3 AND #51), Limtied to 2010 to 2011, in CENTRAL database

Table 104: Cochrane (CENTRAL) database search strategy (searched on 27.02.12)

#	Search History
1	MeSH descriptor Prostatic Neoplasms, this term only
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
3	(#1 OR #2)
4	MeSH descriptor Fluorouracil, this term only
5	fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flurablastin OR fluracedyl OR fluracil OR fluril OR fluroblastin OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
6	abiraterone OR 'cb 7598' OR cb7598 OR 'abiraterone acetate' OR zytiga
7	aflibercept OR 'vegf trap'
8	as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
9	atrasentan OR xinlay
10	bevacizumab OR avastin
11	cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258 OR jevtana
12	MeSH descriptor Carboplatin, this term only
13	carboplatin OR paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
14	MeSH descriptor Cyclophosphamide, this term only
15	cyclophosphamid* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophospham OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
16	dasatinib OR sprycel OR 'bms 354825' OR bms354825
17	MeSH descriptor Dexamethasone, this term only
18	de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	docetaxel OR taxotere OR 'rp 56976' OR rp56976
20	MeSH descriptor Doxorubicin, this term only
21	doxorubicin OR adr OR 'chloridrato de doxorrubicina' OR adriamycin OR adriacin OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
22	estramustine OR emcyt OR estracyt
23	MeSH descriptor Etoposide, this term only
24	etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
25	MeSH descriptor Hydrocortisone, this term only
26	hydrocortisone OR cortifan AND orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
27	cixutumumab OR 'imc a12'
28	ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
29	satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
30	'mdv 3100' OR mdv3100
31	MeSH descriptor Mitoxantrone, this term only
32	mitoxantrone OR novantrone OR mitozantrone OR dihydroxyanthracenedione OR mitroxone OR neotalem OR onkotrone OR pralifan OR dhad OR dhaq
33	MeSH descriptor Paclitaxel, this term only
34	paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
35	MeSH descriptor Epothilones, this term only
36	epothilone OR patupilone OR epo906
37	MeSH descriptor Prednisolone, this term only
38	prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
39	MeSH descriptor Prednisone, this term only

#	Search History
40	prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
41	provenge OR 'sipuleucel t'
42	sunitinib OR sutent OR su011248 OR su11248
43	MeSH descriptor Vinblastine, this term only
44	vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
45	vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
46	'zd 4054' OR zd4054 OR zibotentan
47	MeSH descriptor Strontium, this term only
48	strontium OR metastron OR sr89
49	'zoledronic acid' OR zoledronate OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
50	alpharadin OR ‘radium 223’ OR ‘radium-223’
51	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)
52	(#3 AND #51), from 2011 to 2012, in CENTRAL database
53	#3 AND #50, in CENTRAL database
54	#52 OR #53

Table 105: Cochrane (CENTRAL) database search strategy (searched 27.09.12)

#	Search History
1	MeSH descriptor Prostatic Neoplasms, this term only
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
3	(#1 OR #2)
4	MeSH descriptor Fluorouracil, this term only
5	fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flurablastin OR fluracedyl OR fluracil OR fluril OR fluroblastin OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
6	abiraterone OR 'cb 7598' OR cb7598 OR 'abiraterone acetate' OR zytiga
7	aflibercept OR 'vegf trap'
8	as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
9	atrasentan OR xinlay
10	bevacizumab OR avastin
11	cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258 OR jevtana
12	MeSH descriptor Carboplatin, this term only
13	carboplatin OR paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
14	MeSH descriptor Cyclophosphamide, this term only
15	cyclophosphamid* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophospham OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
16	dasatinib OR sprycel OR 'bms 354825' OR bms354825
17	MeSH descriptor Dexamethasone, this term only
18	de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	docetaxel OR taxotere OR 'rp 56976' OR rp56976
20	MeSH descriptor Doxorubicin, this term only
21	doxorubicin OR adr OR 'chloridrato de doxorrubicina' OR adriamycin OR adriacin OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
22	estramustine OR emcyt OR estracyt
23	MeSH descriptor Etoposide, this term only
24	etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
25	MeSH descriptor Hydrocortisone, this term only

#	Search History
26	hydrocortisone OR cortifan AND orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
27	cixutumumab OR 'imc a12'
28	ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
29	satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
30	'mdv 3100' OR mdv3100 OR Enzalutamide OR Xtandi
31	MeSH descriptor Mitoxantrone, this term only
32	mitoxantrone OR novantrone OR mitozantrone OR dihydroxyanthracenedione OR mitroxone OR neotalem OR onkotrone OR pralifan OR dhad OR dhaq
33	MeSH descriptor Paclitaxel, this term only
34	paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
35	MeSH descriptor Epothilones, this term only
36	epothilone OR patupilone OR epo906
37	MeSH descriptor Prednisolone, this term only
38	prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
39	MeSH descriptor Prednisone, this term only
40	prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
41	provenge OR 'sipuleucel t'
42	sunitinib OR sutent OR su011248 OR su11248
43	MeSH descriptor Vinblastine, this term only
44	vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
45	vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
46	'zd 4054' OR zd4054 OR zibotentan
47	MeSH descriptor Strontium, this term only
48	strontium OR metastron OR sr89
49	'zoledronic acid' OR zoledronate OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
50	alpharadin OR ‘radium 223’ OR ‘radium-223’
51	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)
52	(#3 AND #51), from 2012 to 2012, in CENTRAL database

Table 106: Cochrane (CENTRAL) database search strategy (searched 30.05.13)

#	Search History
1	MeSH descriptor Prostatic Neoplasms, this term only
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
3	(#1 OR #2)
4	MeSH descriptor Fluorouracil, this term only
5	fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flurablastin OR fluracedyl OR fluracil OR fluril OR fluroblastin OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
6	abiraterone OR 'cb 7598' OR cb7598 OR 'abiraterone acetate' OR zytiga
7	aflibercept OR 'vegf trap'
8	as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
9	atrasentan OR xinlay
10	bevacizumab OR avastin
11	cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258 OR jevtana
12	MeSH descriptor Carboplatin, this term only
13	carboplatin OR paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
14	MeSH descriptor Cyclophosphamide, this term only
15	cyclophosphamid* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophospham OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
16	dasatinib OR sprycel OR 'bms 354825' OR bms354825

#	Search History
17	MeSH descriptor Dexamethasone, this term only
18	de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	docetaxel OR taxotere OR 'rp 56976' OR rp56976
20	MeSH descriptor Doxorubicin, this term only
21	doxorubicin OR adr OR 'chloridrato de doxorrubicina' OR adriamycin OR adriacin OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
22	estramustine OR emcyt OR estracyt
23	MeSH descriptor Etoposide, this term only
24	etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
25	MeSH descriptor Hydrocortisone, this term only
26	hydrocortisone OR cortifan AND orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
27	cixutumumab OR 'imc a12'
28	ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
29	satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
30	'mdv 3100' OR mdv3100 OR Enzalutamide OR Xtandi
31	MeSH descriptor Mitoxantrone, this term only
32	mitoxantrone OR novantrone OR mitozantrone OR dihydroxyanthracenedione OR mitroxone OR neotalem OR onkotrone OR pralifan OR dhad OR dhaq
33	MeSH descriptor Paclitaxel, this term only
34	paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
35	MeSH descriptor Epothilones, this term only
36	epothilone OR patupilone OR epo906
37	MeSH descriptor Prednisolone, this term only
38	prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
39	MeSH descriptor Prednisone, this term only
40	prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
41	provenge OR 'sipuleucel t'
42	sunitinib OR sutent OR su011248 OR su11248
43	MeSH descriptor Vinblastine, this term only
44	vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
45	vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
46	'zd 4054' OR zd4054 OR zibotentan
47	MeSH descriptor Strontium, this term only
48	strontium OR metastron OR sr89
49	'zoledronic acid' OR zoledronate OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
50	alpharadin OR ‘radium 223’ OR ‘radium-223’
51	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)
52	(#3 AND #51), from 2012 to 2013, in CENTRAL database

Table 107: Cochrane (CENTRAL) database search strategy (searched 02.09.13)

#	Search History
1	MeSH descriptor Prostatic Neoplasms, this term only
2	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
3	(#1 OR #2)
4	MeSH descriptor Fluorouracil, this term only

#	Search History
5	fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flurablastin OR fluracedyl OR fluracil OR fluril OR fluroblastin OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
6	abiraterone OR 'cb 7598' OR cb7598 OR 'abiraterone acetate' OR zytiga
7	aflibercept OR 'vegf trap'
8	as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
9	atrasentan OR xinlay
10	bevacizumab OR avastin
11	cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258 OR jevtana
12	MeSH descriptor Carboplatin, this term only
13	carboplatin OR paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
14	MeSH descriptor Cyclophosphamide, this term only
15	cyclophosphamid* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophospham OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
16	dasatinib OR sprycel OR 'bms 354825' OR bms354825
17	MeSH descriptor Dexamethasone, this term only
18	de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	docetaxel OR taxotere OR 'rp 56976' OR rp56976
20	MeSH descriptor Doxorubicin, this term only
21	doxorubicin OR adr OR 'chloridrato de doxorrubicina' OR adriamycin OR adriacin OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
22	estramustine OR emcyt OR estracyt
23	MeSH descriptor Etoposide, this term only
24	etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
25	MeSH descriptor Hydrocortisone, this term only
26	hydrocortisone OR cortifan AND orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
27	cixutumumab OR 'imc a12'
28	ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
29	satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
30	'mdv 3100' OR mdv3100 OR Enzalutamide OR Xtandi
31	MeSH descriptor Mitoxantrone, this term only
32	mitoxantrone OR novantrone OR mitozantrone OR dihydroxyanthracenedione OR mitroxone OR neotalem OR onkotrone OR pralifan OR dhad OR dhaq
33	MeSH descriptor Paclitaxel, this term only
34	paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
35	MeSH descriptor Epothilones, this term only
36	epothilone OR patupilone OR epo906
37	MeSH descriptor Prednisolone, this term only
38	prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
39	MeSH descriptor Prednisone, this term only
40	prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
41	provenge OR 'sipuleucel t'
42	sunitinib OR sutent OR su011248 OR su11248
43	MeSH descriptor Vinblastine, this term only
44	vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
45	vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
46	'zd 4054' OR zd4054 OR zibotentan

#	Search History
47	MeSH descriptor Strontium, this term only
48	strontium OR metastron OR sr89
49	'zoledronic acid' OR zoledronate OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
50	alpharadin OR 'radium 223' OR 'radium-223'
51	(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50)
52	(#3 AND #51), from 2012 to 2013, in CENTRAL database

10.2.4.3 MEDLINE In-process search strategies

Table 108: MEDLINE In-process search strategy (searched on 30.05.11)

#	Search history
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotronei OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyte
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100
21	Search aflibercept OR 'vegf trap'
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258

#	Search history
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010'
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35
37	Search #3 AND #36
38	Search #37 AND in process[sb]
Error rectification facet†	
39	Search prostat*
40	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
41	Search #39 AND #40
42	Search mitoxantrone OR mitozantrone
43	Search flurablastin OR fluroblastin
44	Search dihydroxyanthracenedione
45	Search onkotrone
46	Search #42 OR #43 OR #44 OR #45
47	Search #41 AND #46 AND in process [sb]
48	Search (#41 AND #46) AND in process [sb] Limits: Publication Date from 2011/05/30 to 2011/07/19
49	Search #47 NOT #48
50	Search #49 NOT #38

†An error in search terms used for interventions was noted during quality assurance process. The updated searches were conducted on 19.07.11 to investigate impact of this error on overall search results. One additional study was retrieved which did not meet inclusion criteria for this review. Therefore, there was no implication on overall search result.

Table 109: MEDLINE In-process search strategy (searched on 27.02.12)

#	Search history
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotrone OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyt
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone

#	Search history
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100
21	Search aflibercept OR vegf trap
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404 OR jevtana
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054 OR zibotentan
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search alpharadin OR ‘radium 223’ OR ‘radium-223’
37	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
37	Search #3 AND #37
38	Search #37 AND in process[sb]

Table 110: MEDLINE In-process search strategy (searched on 27.09.12)

#	Search history
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotrone OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyt
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR ‘dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid

#	Search history
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100 OR enzalutamide OR xtandi
21	Search aflibercept OR vegf trap
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404 OR jevtana
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054 OR zibotentan
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search alpharadin OR ‘radium 223’ OR ‘radium-223’
37	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38	Search #3 AND #37
39	Search #38 AND in process[sb]

Table 111: MEDLINE In-process search strategy (searched on 30.05.13)

#	Search history
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotrone OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyt
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'

#	Search history
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100 OR enzalutamide OR xtandi
21	Search aflibercept OR vegf trap
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404 OR jevtana
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054 OR zibotentan
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search alpharadin OR ‘radium 223’ OR ‘radium-223’
37	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38	Search #3 AND #37
39	Search #38 AND in process[sb]

Table 112: MEDLINE In-process search strategy (searched on 02.09.13)

#	Search history
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotrone OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyt
7	Search fluorouracil OR 'fluoro uracil’ OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR ‘wr 138719'

#	Search history
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100 OR enzalutamide OR xtandi
21	Search aflibercept OR vegf trap
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404 OR jevtana
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054 OR zibotentan
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010' OR yervoy
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search alpharadin OR ‘radium 223’ OR ‘radium-223’
37	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38	Search #3 AND #37
39	Search #38 AND in process[sb]

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

The following conference proceedings were searched to supplement the search of the electronic literature databases: ASCO annual meeting, EAU, ASCO GU, AUA and ESMO. In the original systematic review, conference proceedings were searched from 2006 to a cut-off date of 08.06.11. The proceedings of conferences conducted in 2006–2013 were searched up to 31.08.13.

Unpublished follow-up data from Janssen related to the COU-AA-302 study were also included in the systematic review.

10.2.6 The inclusion and exclusion criteria.

Table 113: 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 was restricted to match the stated decision problem for the treatment of patients with mCRPC • Since prostate cancer is a disease of adults only, studies including children or adolescents were excluded
	Interventions 5-fluorouracil, abiraterone, alpharadin, aflibercept, AS1404, atrasentan, bevacizumab, cabazitaxel, carboplatin, cyclophosphamide, dasatinib, dexamethasone, docetaxel, doxorubicin, estramustine, etoposide, hydrocortisone, IMC-A12, ipilumumab, JM216, MDV3100, mitoxantrone, paclitaxel, patupilone, prednisone/prednisolone, provenge, sunitinib, vinblastine, vinorelbine, zibotentan	• 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 best supportive care. These comparators were selected to potentially enable the inclusion of all relevant citations • Exclusion on the basis of comparator was only applied to RCTs, as RCTs making other comparisons would not provide data of relevance • Observational studies and non-RCTs were included regardless of the comparator treatment evaluated
	Study design RCTs Non-RCTs Single-arm interventional studies/uncontrolled trials Observational studies, including: • Cohort studies (prospective or retrospective) • Case-control studies • Cross sectional study/survey • Hospital records and database studies	• 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
	Language restrictions English only	• The restriction would not limit results substantially due to data availability in English language
	Publication timeframe No date limit for publications Last 6 years for hand searches	• Studies which are presented at conferences are usually published in journals within 6 years

	Studies should report ≥1 of the following outcomes of interest: • OS and/or PFS • Time to progression (according to PSA and RECIST criteria) • Response rate (according to PSA and RECIST criteria) • Duration of response • PSA measurements • QoL (EORTC-QLQC30 or EQ-5D or FACT-P and its subscale • BPI and/or PPI • Bone pain • Pain response • Time to pain progression • Time to opiate use • VAS pain score • Analgesic score • Time to first SRE • SMR • Vertebral and/or non-vertebral fractures • AEs and/or tolerability	• Studies not reporting 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 No subgroup analysis for metastatic disease **Study design** Case studies Case series Case reports **Phase I** **Dose-ranging studies**	• Studies reporting no subgroup data for the population of interest (mCRPC) were not included. However, studies including a 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

AE, adverse event; BPI, brief pain inventory; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D, EuroQoL Five Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PPI, present pain intensity; PSA, prostate-specific antigen; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria In Solid Tumors; SMR, skeletal morbidity rate; SRE, skeletal-related event; VAS, visual analogue scale.

10.2.7 The data abstraction strategy.

Bibliographic details and abstracts of all the citations detected by the literature search were downloaded into a systematic review database.

First pass of citations
Citations were first screened based on the abstract supplied with each citation. Citations that did not match the eligibility criteria were excluded at this ‘first pass’;

while unclear citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded at the first pass stage. Full-text copies of all references that could potentially meet the eligibility criteria were ordered.

Second pass of citations
The eligibility criteria were applied to the full-text citations. Each full-text was screened for inclusion in the review. All studies included after the second pass were extracted to the data extraction grids.

Extraction strategy
Data from the included trials were extracted into the HERON Systematic Review Database (SRDB). Where more than one publication describing a single trial was identified, the data were compiled into a single entry in the data extraction table to avoid double counting of patients. Each publication was referenced in the table to recognise that more than one publication may have contributed to the entry.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 114: Quality assessment of COU-AA-302

Study question	How is the question addressed in the study?	Grade
Was randomisation carried out appropriately?	The randomisation schedule was generated by an independent statistician at Almac Clinical Technologies. Patients were assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Patient eligibility was verified by the investigators, who then entered the stratification factor (i.e. baseline ECOG PS grade [0 versus 1]) into the Almac IWRS/IVRS system.	Yes
Was the concealment of treatment allocation adequate?	All patients, family members, study personnel (at the study site, the sponsor, or participating Clinical Research Organization), and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the exception of the circumstances described in the text below regarding blinding of treatment allocation. The matched placebo tablets given to patients in the placebo arm were also visually indistinguishable from the abiraterone acetate tablets.	Yes[a]
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	With a few exceptions, demographics and disease characteristics were balanced between the two treatment groups. The few differences in demographics and disease characteristics were not considered clinically relevant.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	All patients, family members, study personnel (at the study site, the sponsor, or participating Clinical Research Organization), and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the following exceptions: The Independent Biostatistician and Independent Statistical Programmer (employed by Novella) responsible for preparing interim tables, listings, and graphs for IDMC review who had no other responsibilities associated with the study. The IDMC, in order to evaluate whether the study should be stopped early for efficacy/futility or safety. Laboratory personnel performing plasma concentration assays for pharmacokinetic analysis. The Independent Biostatistician provided laboratory personnel with patients' randomisation codes without sponsor involvement. This process was undertaken to avoid futile pharmacokinetic analysis of placebo specimens that did not contain abiraterone. Laboratory personnel received no other data associated with the patients, with the exception of deviation listings pertaining to the collection of the pharmacokinetic samples.	Yes[a]

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No imbalances in dropouts between groups were observed	No imbalances in dropouts between groups were observed
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The clinical study report and associated journal and conference publications for the COU-AA-302 study were available and were reviewed. There was no indication that the clinical study report did not include all the measured outcomes	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population included all patients randomised into the study; patients were to be classified according to assigned treatment group, regardless of the actual treatment received. The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.	Yes

ECOG, Eastern Cooperative Oncology Group; IDMC, Independent Data Monitoring Committee; ITT, intent-to-treat; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; N/A, not applicable; PS, performance status.

[a] It should be noted that an error resulted in the wrong AA study drug tablets being distributed by the sponsor. From 15.12.11 through 29.0312, these tablets were dispensed to 62 subjects assigned to the AAP group at 24 sites in the US and Canada. The affected tablets contained the proper dosage and formulation of AA, but were debossed with the text “AA250.” The correct study tablets were not marked. This error resulted in the possibility that two subjects may have imputed their treatment assignment from the de-bossed tablets 5 days prior to the 20.12.11 cutoff date. The last bottle with de-bossed tablets was dispensed on 29.03.12. The issue was resolved.

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library.**

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.2 The date on which the search was conducted.

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.3 The date span of the search.

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.6 The inclusion and exclusion criteria.

N/A, as indirect or mixed treatment comparisons were not appropriate.

10.4.7 The data abstraction strategy.

N/A, as indirect or mixed treatment comparisons were not appropriate

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

A/A, as indirect or mixed treatment comparisons were not appropriate.

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library.**

The systematic review to identify non-RCT evidence was undertaken in one overarching systematic review as has been previously described in section 0.

10.6.2 The date on which the search was conducted.

Described in section 10.2.2.

10.6.3 The date span of the search.

Described in section 10.2.3.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Described in section 10.2.4.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Described in section 10.2.5.

10.6.6 The inclusion and exclusion criteria.

Described in section 10.2.6.

10.6.7 The data abstraction strategy.

Described in section 10.2.7.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Two non-RCT clinical studies were identified which had been undertaken that support the efficacy and safety of AAP in the treatment of patients with mCRPC after failure of ADT. The quality assessment of these two studies is described in Table 115.

Table 115: Descriptive appraisal of the non-RCT studies considered as part of this submission

Study name	Bias in results	Study question	Methodology	Population and data collection	Statistical methods	Results and confounding factors	Conclusions
COU-AA-001 (and COU-AA-001 EXT)	Yes. The patient population included in the study was broadly defined.	The study clearly defined a specific question.	Enough detail to allow the study to be reproduced. Appropriate methods were used to answer the specified research question and the outcome measures used were appropriate. The methods were accurate and the results reliable.	The population under study was described and recruited adequately and the inclusion/exclusion criteria were sufficiently described. The collection of data was complete enough (in terms of size of population and follow-up period).	The primary objective was to determine the rate of patients demonstrating a ≥50% decline in PSA after 12 weeks of single-agent AA 1,000 mg. Median time to PSA was calculated using the Kaplan–Meier product limit method. Patients were censored if they had reached the end of their participation in the trial, but were otherwise considered. The null hypothesis was a ≥50% PSA reduction rate in 10% of patients; a decline in 30% of patients was the alternative hypothesis.	The results were presented in a clear and useful manner. The tables and graphs were clear and interpretable. Effect of confounding factors was not studied.	The authors provided a clear discussion of the results that lead to a single, specified conclusion in answer to the specified study question. The authors related their results to previous literature in the field. There was consistency between the conclusions and the results presented.
COU-AA-002	No. Patient population was adequately described.	The study clearly addressed the specific question and the study question was specifically stated.	The study methods were clearly described with enough detail to answer the specified question. Outcome measures used were appropriate.	The population under study was described with specific inclusion/exclusion criteria sufficiently described. Details pertaining to recruitment of the study population and collection of the data were reported.	Details of statistical methods used or the type of analysis were adequately reported in the study. Rationale was given for the methodology of analysis used. Factors were reported for model adjustment. No unexplained unusual statistical methods were reported to have been used during the analyses of the data.	Results were appropriately presented to enable understanding. Possible confounding factors were not reported. Results were not due to chance or bias.	Results were adequately discussed. Authors related results to previous literature. Results presented were consistent with the conclusions

PSA, prostate-specific antigen

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **The Cochrane Library.**

AEs were included as an outcome of interest in the overarching systematic review; therefore all RCTs and non-RCTs whereby safety data generation was the primary objective were included and have been previously described in section 0.

10.8.2 The date on which the search was conducted.

Described in section 10.2.2.

10.8.3 The date span of the search.

Described in section 10.2.3.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Described in section 10.2.4.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Described in section 10.2.5.

10.8.6 The inclusion and exclusion criteria.

Described in section 10.2.6.

10.8.7 The data abstraction strategy.

Described in section 10.2.7.

10.9 Appendix 9: Quality assessment of AE data in section 6.9

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

N/A.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **EconLIT**
- **NHS EED.**

The literature databases MEDLINE (including MEDLINE In-Process, Other Non-Indexed Citations), Excerpta Medica Database (Embase), the Cochrane databases, and EconLit were searched. MEDLINE and Embase were searched via the Embase.com interface, MEDLINE In-Process and Other Non-Indexed Citations were searched via the PubMed interface, EconLit was searched via the interface provided by the American Economic Association, and the Cochrane databases were searched via the Cochrane Library's own interface.

10.10.2 The date on which the search was conducted.

The searches were conducted on 02.09.13.

10.10.3 The date span of the search.

The search was limited to material published between 01.01.00 and 02.09.13.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies used for the searches of the electronic literature databases are shown in the following tables.

Table 116: Embase and MEDLINE database search strategy (searched on 20.11.12)

#	Search string
1	'economics'/de
2	'economic aspect'/de
3	'cost'/de
4	'health care cost'/exp OR 'health care cost'
5	'drug cost'/de
6	'hospital cost'/de
7	'socioeconomics'/de
8	'health economics'/de
9	'pharmacoeconomics'/de
10	'fee'/exp
11	'budget'/exp
12	'economic evaluation'/exp
13	'hospital finance'/de OR 'financial management'/de
14	'health care financing'/de
15	'health care utilization'/de

#	Search string
16	'low cost'
17	'high cost'
18	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*
19	fiscal OR funding OR financial OR finance
20	cost NEXT/1 estimate*
21	'cost variable'
22	unit NEXT/1 cost*
23	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti
24	cost* NEAR/3 (treat* OR therap*)
25	health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization)
26	resource NEXT/1 (utilisation OR utilization OR use)
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28	'prostate cancer'/exp
29	'prostate tumor'/de
30	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
31	crpc
32	castrat* NEAR/3 resistant
33	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
34	#32 AND #33
35	#28 OR #29 OR #30 OR #31 OR #34
36	'2,4-dioxo-5-fluoropyrimidine':ab,ti OR '5-fluoro-2,4(1h, 3h)-pyrimidinedione':ab,ti OR '5-fluorouracil':ab,ti OR '5-fluracil':ab,ti OR '5-fu':ab,ti OR accusite:ab,ti OR 'actino-hermal':ab,ti OR adrucil:ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efudex:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR 'fluoro uracil':ab,ti OR fluoroplex:ab,ti OR fluorouracil:ab,ti OR fluouracil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR 'ro 2-9757':ab,ti OR timazin:ab,ti
37	abarelix:ab,ti OR plenaxis:ab,ti OR 'ppi 149':ab,ti OR 'r 3827':ab,ti OR ppi149:ab,ti OR r3827:ab,ti
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti
39	aflibercept:ab,ti OR 'ave0005':ab,ti OR 'vascular endothelial growth factor trap':ab,ti OR 'vegf trap r1r2':ab,ti OR 'vegf trap':ab,ti OR 'vasculotropin trap':ab,ti
40	'2-(p-aminophenyl)-2-ethylglutarimide':ab,ti OR '3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione':ab,ti OR 'alpha-(4-aminophenyl)-alpha-ethylglutarimide':ab,ti OR aminoblastin:ab,ti OR aminoglutethimide:ab,ti OR 'ba-16038':ab,ti OR cytadren:ab,ti OR elipten:ab,ti OR mamomit:ab,ti OR orimenten*:ab,ti OR orimeten:ab,ti OR rodazol:ab,ti
41	'abt 627':ab,ti OR atrasentan:ab,ti OR xinlay:ab,ti OR abt627:ab,ti OR 'a 147627':ab,ti OR a147627:ab,ti OR a1277*:ab,ti OR (a NEXT/1 1277*):ab,ti
42	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'anti-vegf humanized monoclonal antibody':ab,ti OR 'anti-vegf rhumab':ab,ti OR 'recombinant humanized anti-vegf monoclonal antibody':ab,ti OR 'rhumab-vegf':ab,ti
43	bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR 'ici 176334':ab,ti OR ici176334:ab,ti OR raffolutil:ab,ti
44	'1-hydroxy-7beta,10beta-dimethoxy-9-oxo-5beta,20-epoxytax-11-ene-2alpha,4,13alpha-triyl 4-acetate 2-benzoate 13-[(2r,3s)-3-([(tertbutoxy)carbonyl]amino)-2-hydroxy-3-phenylpropanoate]':ab,ti OR cabazitaxel:ab,ti OR 'rpr 116258a':ab,ti OR 'taxoid xrp6258':ab,ti OR xrp6258:ab,ti
45	'(sp-4-2)-diammine[1,1-cyclobutanedicarboxylato(2--)-o,o]platinum':ab,ti OR '1,1-cyclobutanedicarboxylic acid platinum complex':ab,ti OR blastocarb:ab,ti OR carboplatin:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR cbdca:ab,ti OR 'cis-diammine(1,1-cyclobutanedicarboxylato) platinum(ii)':ab,ti OR displata:ab,ti OR ercar:ab,ti OR 'jm-8':ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR paraplat*:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti
46	'nsc 81340':ab,ti OR 'nsc 81430':ab,ti OR nsc81340:ab,ti OR nsc81430:ab,ti OR 'sh 714':ab,ti OR sh714:ab,ti OR sinovir:ab,ti OR virilit:ab,ti OR cyproterone:ab,ti
47	'corticosteroid'/exp
48	'antiandrogen'/exp
49	'gonadorelin agonist'/exp OR 'lhrh agonist'
50	'cancer immunotherapy'/exp
51	dasatinib:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti OR sprycel:ab,ti
52	degarelix:ab,ti OR fe200486:ab,ti OR 'fe 200486':ab,ti
53	dexamethasone:ab,ti OR 'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflog*:ab,ti OR arcodex*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR (dacort* NEAR/1 fue*):ab,ti OR dalalone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR decacort*:ab,ti OR dekacort*:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameto*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR d?xamethasone:ab,ti OR esacortene:ab,ti OR 'ex s1':ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR (fluor* NEAR/1 predniso*):ab,ti OR fluormethylpredniso*:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR dexa*:ab,ti OR hexadecad*:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isopto*:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazon*:ab,ti OR 'metisone lafi':ab,ti OR millicorten*:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR opticort*:ab,ti OR oradex*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR 'predni f tablinen':ab,ti OR 'prednisolone f':ab,ti OR prodex*:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti OR decadeltosona:ab,ti OR decadeltosone:ab,ti OR decadion*:ab,ti OR decadran:ab,ti OR decadron*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti

#	Search string
54	'(e)-4,4-(1,2-diethyl-1,2-ethenediyl)bisphenol':ab,ti OR '3, 4-bis(p-hydroxyphenyl)-3-hexene':ab,ti OR acnestrol:ab,ti OR 'alpha,alpha-diethylstilbenediol':ab,ti OR antigestil:ab,ti OR apstil:ab,ti OR boestrol:ab,ti OR bufon:ab,ti OR 'cyren a':ab,ti OR des:ab,ti OR diastyl:ab,ti OR diethylstilbenediol:ab,ti OR diethylstilbestrolum:ab,ti OR diethylstilbestrol:ab,ti OR diethylstilboestrol:ab,ti OR distilbene:ab,ti OR domestrol:ab,ti OR estrobene:ab,ti OR estromenin:ab,ti OR estrosyn:ab,ti OR fonatol:ab,ti OR grafestrol:ab,ti OR makarol:ab,ti OR microest:ab,ti OR milestrol:ab,ti OR 'neo-oestronol i':ab,ti OR oestrogeni*:ab,ti OR oestromenin:ab,ti OR oestromensyl:ab,ti OR oestromon:ab,ti OR sexocretin:ab,ti OR sibol:ab,ti OR stilbestro*:ab,ti OR stilbetin:ab,ti OR stilboefral:ab,ti OR stilboestrol:ab,ti OR stilkap:ab,ti OR synestrin:ab,ti OR synthoestrin:ab,ti OR vagestrol:ab,ti OR hexanestrol:ab,ti OR hexestrofen:ab,ti OR hexital:ab,ti OR hexron:ab,ti OR hexypheen:ab,ti OR 'hi bestrol':ab,ti OR 'hormoestrol':ab,ti OR menostilbene:ab,ti OR 'meso hexestrol':ab,ti OR mesohexestrol:ab,ti OR micrest:ab,ti OR 'neo estranol':ab,ti OR 'nsc 3070':ab,ti OR 'nsc 35752':ab,ti OR 'nsc 9894':ab,ti OR oekolp:ab,ti OR oestrostilben:ab,ti OR oestrosyntal:ab,ti OR orestrol:ab,ti OR ovendosyn:ab,ti OR pabestrol:ab,ti OR pabestrosalve:ab,ti OR palestrol:ab,ti OR proestrin:ab,ti OR serral:ab,ti
55	docetaxel:ab,ti OR taxotere:ab,ti
56	'(8s-cis)-10-[(3-amino-2,3,6-trideoxy-alpha-l-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione':ab,ti OR '14-hydroxydaunomycin':ab,ti OR doxorubicin:ab,ti OR 'hydroxyl daunorubicin':ab,ti OR adriablastin*:ab,ti OR adriacin:ab,ti OR adriam?cina:ab,ti OR adriamycin:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR dexorubicin:ab,ti OR 'dox sl':ab,ti OR doxil:ab,ti OR doxorubicin*:ab,ti OR 'fi 106':ab,ti OR lipodox:ab,ti OR 'liposomal doxorubicin':ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR 'pegylated liposomal doxorubicin':ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti
57	dutasteride:ab,ti OR 'gg 745':ab,ti OR 'gg745':ab,ti OR avodart:ab,ti OR avolve:ab,ti OR advodart:ab,ti OR duagen:ab,ti OR 'gi 198745':ab,ti OR gi198745*:ab,ti
58	e7389:ab,ti OR 'e 7389':ab,ti OR eribulin:ab,ti OR 'halichondrin b analog':ab,ti
59	estramustine:ab,ti OR 'leo 275':ab,ti OR 'leo 462':ab,ti OR 'nsc 89199':ab,ti OR 'ro 21 8837':ab,ti OR 'ro 22 2296 000':ab,ti OR leo275:ab,ti OR leo462:ab,ti OR nsc89199:ab,ti OR ro218837:ab,ti OR ro222296000:ab,ti
60	'4-demethylepipodophyllotoxin 9-[4,6-o-ethylidene-beta-d-glucopyranoside':ab,ti OR 'demethyl epipodophyllotoxin ethylidine glucoside':ab,ti OR epeg:ab,ti OR etoposide:ab,ti OR vepesid:ab,ti OR 'vp 16-213':ab,ti OR etomedac:ab,ti OR etopol:ab,ti OR lastet:ab,ti OR 'nk 171':ab,ti OR 'nsc 141540':ab,ti OR toposar:ab,ti OR vepesid*:ab,ti
61	'(5alpha,17beta)-n-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide':ab,ti OR 'chibro-proscar':ab,ti OR finasteride:ab,ti OR finastid:ab,ti OR 'mk 906':ab,ti OR 'pro-cure':ab,ti OR propecia:ab,ti OR propeshia:ab,ti OR proscar:ab,ti OR prostide:ab,ti OR urprosan:ab,ti OR 'ym 152':ab,ti
62	flutamide:ab,ti OR apimid:ab,ti OR chimax:ab,ti OR eulexine:ab,ti OR flucinome:ab,ti OR flucinom:ab,ti OR flugerel:ab,ti OR fluken:ab,ti OR flulem:ab,ti OR 'fluta-gry':ab,ti OR flutabene:ab,ti OR flutacan:ab,ti OR flutamex:ab,ti OR flutamin:ab,ti OR flutan:ab,ti OR flutaplex:ab,ti OR flut:ab,ti OR fugerel:ab,ti OR grisetin:ab,ti OR oncosal:ab,ti OR profamid:ab,ti OR prostacur:ab,ti OR prostadirex:ab,ti OR prostica:ab,ti OR prostogenat:ab,ti OR 'sch 13521':ab,ti OR sch13521:ab,ti OR tafenil:ab,ti OR tecnoflut:ab,ti OR testotard:ab,ti OR drogenil:ab,ti OR euflex:ab,ti OR eulexin:ab,ti OR flumid:ab,ti OR niftolid:ab,ti OR niphtholid:ab,ti OR sebatrol:ab,ti
63	goserelin:ab,ti OR 'ici-118630':ab,ti OR 'ici 118 630':ab,ti OR 'ici 118630':ab,ti OR ici118630:ab,ti OR zoladex:ab,ti
64	'(11beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione':ab,ti OR 'aeroseb-hc':ab,ti OR 'barseb hc':ab,ti OR cetacort:ab,ti OR 'cort-dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortifan:ab,ti OR cortisol:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR domolene:ab,ti OR eldecort:ab,ti OR hautosone:ab,ti OR 'heb-cort':ab,ti OR hydrocortisone:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR 'komed-hc':ab,ti OR nutracort:ab,ti OR proctocort:ab,ti OR rectoid:ab,ti OR therapeutic:ab,ti AND hydrocortisone:ab,ti OR alphaderm:ab,ti OR barseb:ab,ti OR cetacort:ab,ti OR cobadex:ab,ti OR 'compound f':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortibel:ab,ti OR cortifan:ab,ti OR cortifoam:ab,ti OR cortiment:ab,ti OR cortiphate:ab,ti OR cortisol*:ab,ti OR cortoderm:ab,ti OR cortril:ab,ti OR dermolate:ab,ti OR dioderm:ab,ti OR duomedihaler:ab,ti OR 'ef cortelan':ab,ti OR efcortelan:ab,ti OR egocort:ab,ti OR eksalb:ab,ti OR eldecort:ab,ti OR ficortril:ab,ti OR hebcort:ab,ti OR hycort:ab,ti OR hydracort:ab,ti OR hydrasson:ab,ti OR 'hydro ricortex':ab,ti OR hydrocort:ab,ti OR hydrocorticosteroid:ab,ti OR hydrocortisate:ab,ti OR hydrocortis*:ab,ti OR hydrocortone:ab,ti OR hydroderm:ab,ti OR hysone:ab,ti OR hytone:ab,ti OR incortin:ab,ti OR medihaler:ab,ti OR mildison:ab,ti OR munitren:ab,ti AND 'neo cortef':ab,ti OR neocortef:ab,ti OR novohydrocort:ab,ti OR 'nsc 10483':ab,ti OR 'nsc 741':ab,ti OR nutracort:ab,ti OR otosone:ab,ti OR penecort:ab,ti OR prepcort:ab,ti OR proctocort:ab,ti OR proctosone:ab,ti OR rectocort:ab,ti OR schericur:ab,ti OR 'scherosone f':ab,ti OR 'solu cortef':ab,ti OR synacort:ab,ti OR vasocort:ab,ti
65	'anti-cytotoxic t-lymphocyte-associated antigen-4 monoclonal antibody':ab,ti OR ipilimumab:ab,ti OR 'mdx-010':ab,ti OR 'mdx-ctla4':ab,ti OR 'bms 734016':ab,ti
66	jm216:ab,ti OR 'jm 216':ab,ti
67	ketoconazole:ab,ti OR fungarest:ab,ti OR fungoral:ab,ti OR ketoderm:ab,ti OR ketoisdin:ab,ti OR nizoral:ab,ti OR orifungal:ab,ti OR panfungol:ab,ti OR xolegel:ab,ti OR anisole:ab,ti OR cetonax:ab,ti OR 'dio 902':ab,ti OR dio902:ab,ti OR 'kw 1414':ab,ti OR kw1414:ab,ti OR micoral:ab,ti OR nisoral:ab,ti OR oxocanazole:ab,ti OR oxoconazole:ab,ti OR 'r 41 400':ab,ti OR r41400:ab,ti OR terzolin:ab,ti
68	leuprolide:ab,ti OR leuprorelin:ab,ti OR leuplin:ab,ti OR leupro*:ab,ti OR lucrin:ab,ti OR lupride:ab,ti OR lupron:ab,ti OR procrin:ab,ti OR prostap:ab,ti OR tap144:ab,ti OR 'tap 144':ab,ti
69	mdv3100:ab,ti OR 'mdv3100':ab,ti
70	megastrol:ab,ti
71	mitoxantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mito?antrone:ab,ti OR novanthron:ab,ti OR novantron*:ab,ti OR 'now 85 34':ab,ti OR 'now 8534':ab,ti OR now8534:ab,ti OR 'nsc 279836':ab,ti OR 'nsc 301739':ab,ti OR 'nsc 301739d':ab,ti OR nsc279836:ab,ti OR nsc301739:ab,ti OR nsc301739d:ab,ti
72	nilutamide:ab,ti OR anandron:ab,ti OR nilandron:ab,ti OR anadron:ab,ti OR nitulamide:ab,ti OR 'rn 23908':ab,ti OR 'ru 23908':ab,ti OR rn23908:ab,ti OR ru23908:ab,ti
73	'abi 007':ab,ti OR 'abi007':ab,ti OR abraxane:ab,ti OR 'bms 181339':ab,ti OR coroxane:ab,ti OR genexol:ab,ti OR hunxol:ab,ti OR intaxel:ab,ti OR 'nsc 125973':ab,ti OR paxceed:ab,ti OR paclitaxel:ab,ti OR paxene:ab,ti OR taxol:ab,ti OR yewtaxan:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti

#	Search string
74	'pamidronic acid':ab,ti OR pamidronate:ab,ti OR aredia:ab,ti OR aminomux:ab,ti OR 'gcp-23339a':ab,ti
75	prednison*:ab,ti OR prednisolon*:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR 'de cortin':ab,ti OR decortin:ab,ti OR 'de cortisyl':ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR 'delta(1)-cortisone':ab,ti OR 'delta-dome':ab,ti OR deltacortene:ab,ti OR deltacortisone:ab,ti OR deltadehydrocortisone:ab,ti OR deltasone:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR lisacort:ab,ti OR 'meprosona-f':ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR 'panasol-s':ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicorten:ab,ti OR predicor:ab,ti OR 'prednicen-m':ab,ti OR prednicort:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednisone:ab,ti OR prednisonum:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti OR 'sk-prednisone':ab,ti OR sterapred:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR decortancyl:ab,ti OR dekortin:ab,ti OR delitisone:ab,ti OR 'delta cortelan':ab,ti OR 'delta cortisone':ab,ti OR 'delta dome':ab,ti OR 'delta e':ab,ti OR 'delta prenovis':ab,ti OR deltacorten:ab,ti OR deltacortone:ab,ti OR 'di adreson':ab,ti OR diadreson:ab,ti OR encorton*:ab,ti OR enkorton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone:ab,ti OR orisane:ab,ti OR precort:ab,ti OR precortal:ab,ti OR pronison*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti
76	samarium:ab,ti
77	sipuleucelt:ab,ti OR 'apc8015 vaccine':ab,ti OR 'apc8015':ab,ti OR 'pa2024 (pap/gm-csf)-loaded dendritic cell vaccine':ab,ti OR provenge:ab,ti OR 'sipuleucel-t':ab,ti OR 'apc 8015':ab,ti
78	strontium:ab,ti
79	'tak-700':ab,ti OR 'tak 700':ab,ti OR 'tak700':ab,ti
80	triptorelin:ab,ti OR '6-d-tryptophan-lh-rh':ab,ti OR '6-d-tryptophanluteinizing hormone-releasing factor':ab,ti OR 'ay-25650':ab,ti OR 'cl-118,532':ab,ti OR 'decapeptyl':ab,ti OR detryptoreline:ab,ti OR '[d trp 6] lhrh':ab,ti OR 'arvekap':ab,ti OR 'ay 25650':ab,ti OR 'ay25650':ab,ti OR 'd trp 6 lhrh':ab,ti OR 'd trp 6 luteinizing hormone releasing hormone':ab,ti OR 'gonadorelin [6 dextro tryptophan]':ab,ti OR 'gonadotropin releasing hormone [6 dextro tryptophan]':ab,ti OR 'lhrh (d trp 6)':ab,ti OR 'lhrh [6 dextro tryptophan]':ab,ti OR 'luteinizing hormone releasing hormone [6 dextro tryptophan]':ab,ti OR trelstar:ab,ti OR 'trelstar la':ab,ti OR tryptorelin:ab,ti
81	'le 29060':ab,ti OR 'le29060':ab,ti OR 'leukoblastin':ab,ti OR rozevin:ab,ti OR 'vin blastine':ab,ti OR vinblastin*:ab,ti OR vincaleucoblastin*:ab,ti OR vincaleukoblastin*:ab,ti OR vincoblastin*:ab,ti OR vincoleucoblastin*:ab,ti OR vincoleukoblastin*:ab,ti OR vinleucoblastine:ab,ti OR vlb:ab,ti
82	navelbine:ab,ti OR vinorelbine:ab,ti OR '3,4-didehydro-4-deoxy-c-norvincaleukoblastine':ab,ti OR '5-nor-anhydrovinblastine':ab,ti OR dihydroxydeoxynorvinkaleukoblastine:ab,ti OR 'nor-5-anhydrovinblastine':ab,ti
83	zd4054:ab,ti OR 'zd 4054':ab,ti OR zibotentan:ab,ti OR 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide':ab,ti
84	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR reclast:ab,ti OR 'zol 446':ab,ti OR 'cgp 42446':ab,ti
85	'5, 6 dimethyl 9 oxo 9h xanthene 4 acetic acid':ab,ti OR dmxaa:ab,ti OR 'as 1404':ab,ti OR as1404:ab,ti OR 'asa 404':ab,ti OR asa404:ab,ti OR 'nsc 640488':ab,ti OR nsc640488:ab,ti
86	'imc a12':ab,ti OR 'imc ? a12':ab,ti OR cixutumumab:ab,ti OR 'anti-igf-1r recombinant monoclonal antibody imc-a12':ab,ti
87	patupilone:ab,ti OR 'epo 906':ab,ti OR epo906:ab,ti OR 'epothilon b':ab,ti
88	sunitinib:ab,ti OR 'pha 2909040ad':ab,ti OR pha2909040ad:ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR su011248:ab,ti OR su10398:ab,ti OR su11248:ab,ti OR sutent:ab,ti
89	'cab':ab,ti OR 'complete androgen blockade':ab,ti
90	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
91	#27 AND #35 AND #90
92	#27 AND #35 AND #90 AND [14-12-2009]/sd NOT [9-6-2011]/sd

Table 117: Embase and MEDLINE database search strategy (searched on 30.05.13)

#	Search string
1	'economics'/de
2	'economic aspect'/de
3	'cost'/de
4	'health care cost'/exp OR 'health care cost'
5	'drug cost'/de
6	'hospital cost'/de
7	'socioeconomics'/de
8	'health economics'/de
9	'pharmacoeconomics'/de
10	'fee'/exp
11	'budget'/exp
12	'economic evaluation'/exp
13	'hospital finance'/de OR 'financial management'/de
14	'health care financing'/de
15	'health care utilization'/de
16	'low cost'
17	'high cost'

#	Search string
18	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*
19	fiscal OR funding OR financial OR finance
20	cost NEXT/1 estimate*
21	'cost variable'
22	unit NEXT/1 cost*
23	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti
24	cost* NEAR/3 (treat* OR therap*)
25	health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization)
26	resource NEXT/1 (utilisation OR utilization OR use)
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28	'prostate cancer'/exp
29	'prostate tumor'/de
30	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
31	crpc
32	castrat* NEAR/3 resistant
33	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
34	#32 AND #33
35	#28 OR #29 OR #30 OR #31 OR #34
36	'2,4-dioxo-5-fluoropyrimidine':ab,ti OR '5-fluoro-2,4(1h, 3h)-pyrimidinedione':ab,ti OR '5-fluorouracil':ab,ti OR '5-fluracil':ab,ti OR '5-fu':ab,ti OR accusite:ab,ti OR 'actino-hermal':ab,ti OR adrucil:ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efudex:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR 'fluoro uracil':ab,ti OR fluoroplex:ab,ti OR fluorouracil:ab,ti OR fluouracil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR 'ro 2-9757':ab,ti OR timazin:ab,ti
37	abarelix:ab,ti OR plenaxis:ab,ti OR 'ppi 149':ab,ti OR 'r 3827':ab,ti OR ppi149:ab,ti OR r3827:ab,ti
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti
39	aflibercept:ab,ti OR 'ave0005':ab,ti OR 'vascular endothelial growth factor trap':ab,ti OR 'vegf trap r1r2':ab,ti OR 'vegf trap':ab,ti OR 'vasculotropin trap':ab,ti
40	'2-(p-aminophenyl)-2-ethylglutarimide':ab,ti OR '3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione':ab,ti OR 'alpha-(4-aminophenyl)-alpha-ethylglutarimide':ab,ti OR aminoblastin:ab,ti OR aminoglutethimide:ab,ti OR 'ba-16038':ab,ti OR cytadren:ab,ti OR elipten:ab,ti OR mamomit:ab,ti OR orimenten*:ab,ti OR orimeten:ab,ti OR rodazol:ab,ti
41	'abt 627':ab,ti OR atrasentan:ab,ti OR xinlay:ab,ti OR abt627:ab,ti OR 'a 147627':ab,ti OR a147627:ab,ti OR a1277*:ab,ti OR (a NEXT/1 1277*):ab,ti
42	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'anti-vegf humanized monoclonal antibody':ab,ti OR 'anti-vegf rhumab':ab,ti OR 'recombinant humanized anti-vegf monoclonal antibody':ab,ti OR 'rhumab-vegf':ab,ti
43	bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR 'ici 176334':ab,ti OR ici176334:ab,ti OR raffolutil:ab,ti
44	'1-hydroxy-7beta,10beta-dimethoxy-9-oxo-5beta,20-epoxytax-11-ene-2alpha,4,13alpha-triyl 4-acetate 2-benzoate 13-[(2r,3s)-3-([(tertbutoxy)carbonyl]amino)-2-hydroxy-3-phenylpropanoate]':ab,ti OR cabazitaxel:ab,ti OR 'rpr 116258a':ab,ti OR 'taxoid xrp6258':ab,ti OR xrp6258:ab,ti
45	'(sp-4-2)-diammine[1,1-cyclobutanedicarboxylato(2--)-o,o]platinum':ab,ti OR '1,1-cyclobutanedicarboxylic acid platinum complex':ab,ti OR blastocarb:ab,ti OR carboplatin:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR cbdca:ab,ti OR 'cis-diammine(1,1-cyclobutanedicarboxylato) platinum(ii)':ab,ti OR displata:ab,ti OR ercar:ab,ti OR 'jm-8':ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR paraplat*:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti
46	'nsc 81340':ab,ti OR 'nsc 81430':ab,ti OR nsc81340:ab,ti OR nsc81430:ab,ti OR 'sh 714':ab,ti OR sh714:ab,ti OR sinovir:ab,ti OR virilit:ab,ti OR cyproterone:ab,ti
47	'corticosteroid'/exp
48	'antiandrogen'/exp
49	'gonadorelin agonist'/exp OR 'lhrh agonist'
50	'cancer immunotherapy'/exp
51	dasatinib:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti OR sprycel:ab,ti
52	degarelix:ab,ti OR fe200486:ab,ti OR 'fe 200486':ab,ti
53	dexamethasone:ab,ti OR 'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflog*:ab,ti OR arcodex*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR (dacort* NEAR/1 fue*):ab,ti OR dalalone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR decacort*:ab,ti OR dekacort*:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameto*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR d?xamethasone:ab,ti OR esacortene:ab,ti OR 'ex s1':ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR (fluor* NEAR/1 predniso*):ab,ti OR fluormethylpredniso*:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR dexa*:ab,ti OR hexadecad*:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isopto*:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazon*:ab,ti OR 'metisone lafi':ab,ti OR millicorten*:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR opticort*:ab,ti OR oradex*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR 'predni f tablinen':ab,ti OR 'prednisolone f':ab,ti OR prodex*:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti OR decadeltosona:ab,ti OR decadeltosone:ab,ti OR decadion*:ab,ti OR decadran:ab,ti OR decadron*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti

#	Search string
54	'(e)-4,4-(1,2-diethyl-1,2-ethenediyl)bisphenol':ab,ti OR '3, 4-bis(p-hydroxyphenyl)-3-hexene':ab,ti OR acnestrol:ab,ti OR 'alpha,alpha-diethylstilbenediol':ab,ti OR antigestil:ab,ti OR apstil:ab,ti OR boestrol:ab,ti OR bufon:ab,ti OR 'cyren a':ab,ti OR des:ab,ti OR diastyl:ab,ti OR diethylstilbenediol:ab,ti OR diethylstilbestrolum:ab,ti OR diethylstilbestrol:ab,ti OR diethylstilboestrol:ab,ti OR distilbene:ab,ti OR domestrol:ab,ti OR estrobene:ab,ti OR estromenin:ab,ti OR estrosyn:ab,ti OR fonatol:ab,ti OR grafestrol:ab,ti OR makarol:ab,ti OR microest:ab,ti OR milestrol:ab,ti OR 'neo-oestronol i':ab,ti OR oestrogeni*:ab,ti OR oestromenin:ab,ti OR oestromensyl:ab,ti OR oestromon:ab,ti OR sexocretin:ab,ti OR sibol:ab,ti OR stilbestro*:ab,ti OR stilbetin:ab,ti OR stilboefral:ab,ti OR stilboestrol:ab,ti OR stilkap:ab,ti OR synestrin:ab,ti OR synthoestrin:ab,ti OR vagestrol:ab,ti OR hexanestrol:ab,ti OR hexestrofen:ab,ti OR hexital:ab,ti OR hexron:ab,ti OR hexypheen:ab,ti OR 'hi bestrol':ab,ti OR 'hormoestrol':ab,ti OR menostilbene:ab,ti OR 'meso hexestrol':ab,ti OR mesohexestrol:ab,ti OR micrest:ab,ti OR 'neo estranol':ab,ti OR 'nsc 3070':ab,ti OR 'nsc 35752':ab,ti OR 'nsc 9894':ab,ti OR oekolp:ab,ti OR oestrostilben:ab,ti OR oestrosyntal:ab,ti OR orestrol:ab,ti OR ovendosyn:ab,ti OR pabestrol:ab,ti OR pabestrosalve:ab,ti OR palestrol:ab,ti OR proestrin:ab,ti OR serral:ab,ti
55	docetaxel:ab,ti OR taxotere:ab,ti
56	'(8s-cis)-10-[(3-amino-2,3,6-trideoxy-alpha-l-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione':ab,ti OR '14-hydroxydaunomycin':ab,ti OR doxorubicin:ab,ti OR 'hydroxyl daunorubicin':ab,ti OR adriablastin*:ab,ti OR adriacin:ab,ti OR adriam?cina:ab,ti OR adriamycin:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR dexorubicin:ab,ti OR 'dox sl':ab,ti OR doxil:ab,ti OR doxorubicin*:ab,ti OR 'fi 106':ab,ti OR lipodox:ab,ti OR 'liposomal doxorubicin':ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR 'pegylated liposomal doxorubicin':ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti
57	dutasteride:ab,ti OR 'gg 745':ab,ti OR 'gg745':ab,ti OR avodart:ab,ti OR avolve:ab,ti OR advodart:ab,ti OR duagen:ab,ti OR 'gi 198745':ab,ti OR gi198745*:ab,ti
58	e7389:ab,ti OR 'e 7389':ab,ti OR eribulin:ab,ti OR 'halichondrin b analog':ab,ti
59	estramustine:ab,ti OR 'leo 275':ab,ti OR 'leo 462':ab,ti OR 'nsc 89199':ab,ti OR 'ro 21 8837':ab,ti OR 'ro 22 2296 000':ab,ti OR leo275:ab,ti OR leo462:ab,ti OR nsc89199:ab,ti OR ro218837:ab,ti OR ro222296000:ab,ti
60	'4-demethylepipodophyllotoxin 9-[4,6-o-ethylidene-beta-d-glucopyranoside':ab,ti OR 'demethyl epipodophyllotoxin ethylidine glucoside':ab,ti OR epeg:ab,ti OR etoposide:ab,ti OR vepesid:ab,ti OR 'vp 16-213':ab,ti OR etomedac:ab,ti OR etopol:ab,ti OR lastet:ab,ti OR 'nk 171':ab,ti OR 'nsc 141540':ab,ti OR toposar:ab,ti OR vepesid*:ab,ti
61	'(5alpha,17beta)-n-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide':ab,ti OR 'chibro-proscar':ab,ti OR finasteride:ab,ti OR finastid:ab,ti OR 'mk 906':ab,ti OR 'pro-cure':ab,ti OR propecia:ab,ti OR propeshia:ab,ti OR proscar:ab,ti OR prostide:ab,ti OR urprosan:ab,ti OR 'ym 152':ab,ti
62	flutamide:ab,ti OR apimid:ab,ti OR chimax:ab,ti OR eulexine:ab,ti OR flucinome:ab,ti OR flucinom:ab,ti OR flugerel:ab,ti OR fluken:ab,ti OR flulem:ab,ti OR 'fluta-gry':ab,ti OR flutabene:ab,ti OR flutacan:ab,ti OR flutamex:ab,ti OR flutamin:ab,ti OR flutan:ab,ti OR flutaplex:ab,ti OR flut:ab,ti OR fugerel:ab,ti OR grisetin:ab,ti OR oncosal:ab,ti OR profamid:ab,ti OR prostacur:ab,ti OR prostadirex:ab,ti OR prostica:ab,ti OR prostogenat:ab,ti OR 'sch 13521':ab,ti OR sch13521:ab,ti OR tafenil:ab,ti OR tecnoflut:ab,ti OR testotard:ab,ti OR drogenil:ab,ti OR euflex:ab,ti OR eulexin:ab,ti OR flumid:ab,ti OR niftolid:ab,ti OR niphtholid:ab,ti OR sebatrol:ab,ti
63	goserelin:ab,ti OR 'ici-118630':ab,ti OR 'ici 118 630':ab,ti OR 'ici 118630':ab,ti OR ici118630:ab,ti OR zoladex:ab,ti
64	'(11beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione':ab,ti OR 'aeroseb-hc':ab,ti OR 'barseb hc':ab,ti OR cetacort:ab,ti OR 'cort-dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortifan:ab,ti OR cortisol:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR domolene:ab,ti OR eldecort:ab,ti OR hautosone:ab,ti OR 'heb-cort':ab,ti OR hydrocortisone:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR 'komed-hc':ab,ti OR nutracort:ab,ti OR proctocort:ab,ti OR rectoid:ab,ti OR therapeutic:ab,ti AND hydrocortisone:ab,ti OR alphaderm:ab,ti OR barseb:ab,ti OR cetacort:ab,ti OR cobadex:ab,ti OR 'compound f':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortibel:ab,ti OR cortifan:ab,ti OR cortifoam:ab,ti OR cortiment:ab,ti OR cortiphate:ab,ti OR cortisol*:ab,ti OR cortoderm:ab,ti OR cortril:ab,ti OR dermolate:ab,ti OR dioderm:ab,ti OR duomedihaler:ab,ti OR 'ef cortelan':ab,ti OR efcortelan:ab,ti OR egocort:ab,ti OR eksalb:ab,ti OR eldecort:ab,ti OR ficortril:ab,ti OR hebcort:ab,ti OR hycort:ab,ti OR hydracort:ab,ti OR hydrasson:ab,ti OR 'hydro ricortex':ab,ti OR hydrocort:ab,ti OR hydrocorticosteroid:ab,ti OR hydrocortisate:ab,ti OR hydrocortis*:ab,ti OR hydrocortone:ab,ti OR hydroderm:ab,ti OR hysone:ab,ti OR hytone:ab,ti OR incortin:ab,ti OR medihaler:ab,ti OR mildison:ab,ti OR munitren:ab,ti AND 'neo cortef':ab,ti OR neocortef:ab,ti OR novohydrocort:ab,ti OR 'nsc 10483':ab,ti OR 'nsc 741':ab,ti OR nutracort:ab,ti OR otosone:ab,ti OR penecort:ab,ti OR prepcort:ab,ti OR proctocort:ab,ti OR proctosone:ab,ti OR rectocort:ab,ti OR schericur:ab,ti OR 'scherosone f':ab,ti OR 'solu cortef':ab,ti OR synacort:ab,ti OR vasocort:ab,ti
65	'anti-cytotoxic t-lymphocyte-associated antigen-4 monoclonal antibody':ab,ti OR ipilimumab:ab,ti OR 'mdx-010':ab,ti OR 'mdx-ctla4':ab,ti OR 'bms 734016':ab,ti
66	jm216:ab,ti OR 'jm 216':ab,ti
67	ketoconazole:ab,ti OR fungarest:ab,ti OR fungoral:ab,ti OR ketoderm:ab,ti OR ketoisdin:ab,ti OR nizoral:ab,ti OR orifungal:ab,ti OR panfungol:ab,ti OR xolegel:ab,ti OR anisole:ab,ti OR cetonax:ab,ti OR 'dio 902':ab,ti OR dio902:ab,ti OR 'kw 1414':ab,ti OR kw1414:ab,ti OR micoral:ab,ti OR nisoral:ab,ti OR oxocanazole:ab,ti OR oxoconazole:ab,ti OR 'r 41 400':ab,ti OR r41400:ab,ti OR terzolin:ab,ti
68	leuprolide:ab,ti OR leuprorelin:ab,ti OR leuplin:ab,ti OR leupro*:ab,ti OR lucrin:ab,ti OR lupride:ab,ti OR lupron:ab,ti OR procrin:ab,ti OR prostap:ab,ti OR tap144:ab,ti OR 'tap 144':ab,ti
69	mdv3100:ab,ti OR 'mdv3100':ab,ti
70	megastrol:ab,ti
71	mitoxantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mito?antrone:ab,ti OR novanthron:ab,ti OR novantron*:ab,ti OR 'now 85 34':ab,ti OR 'now 8534':ab,ti OR now8534:ab,ti OR 'nsc 279836':ab,ti OR 'nsc 301739':ab,ti OR 'nsc 301739d':ab,ti OR nsc279836:ab,ti OR nsc301739:ab,ti OR nsc301739d:ab,ti
72	nilutamide:ab,ti OR anandron:ab,ti OR nilandron:ab,ti OR anadron:ab,ti OR nitulamide:ab,ti OR 'rn 23908':ab,ti OR 'ru 23908':ab,ti OR rn23908:ab,ti OR ru23908:ab,ti
73	'abi 007':ab,ti OR 'abi007':ab,ti OR abraxane:ab,ti OR 'bms 181339':ab,ti OR coroxane:ab,ti OR genexol:ab,ti OR hunxol:ab,ti OR intaxel:ab,ti OR 'nsc 125973':ab,ti OR paxceed:ab,ti OR paclitaxel:ab,ti OR paxene:ab,ti OR taxol:ab,ti OR yewtaxan:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti

#	Search string
74	'pamidronic acid':ab,ti OR pamidronate:ab,ti OR aredia:ab,ti OR aminomux:ab,ti OR 'gcp-23339a':ab,ti
75	prednison*:ab,ti OR prednisolon*:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR 'de cortin':ab,ti OR decortin:ab,ti OR 'de cortisyl':ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR 'delta(1)-cortisone':ab,ti OR 'delta-dome':ab,ti OR deltacortene:ab,ti OR deltacortisone:ab,ti OR deltadehydrocortisone:ab,ti OR deltasone:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR lisacort:ab,ti OR 'meprosona-f':ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR 'panasol-s':ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicorten:ab,ti OR predicor:ab,ti OR 'prednicen-m':ab,ti OR prednicort:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednisone:ab,ti OR prednisonum:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti OR 'sk-prednisone':ab,ti OR sterapred:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR decortancyl:ab,ti OR dekortin:ab,ti OR delitisone:ab,ti OR 'delta cortelan':ab,ti OR 'delta cortisone':ab,ti OR 'delta dome':ab,ti OR 'delta e':ab,ti OR 'delta prenovis':ab,ti OR deltacorten:ab,ti OR deltacortone:ab,ti OR 'di adreson':ab,ti OR diadreson:ab,ti OR encorton*:ab,ti OR enkorton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone:ab,ti OR orisane:ab,ti OR precort:ab,ti OR precortal:ab,ti OR pronison*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti
76	samarium:ab,ti
77	sipuleucelt:ab,ti OR 'apc8015 vaccine':ab,ti OR 'apc8015':ab,ti OR 'pa2024 (pap/gm-csf)-loaded dendritic cell vaccine':ab,ti OR provenge:ab,ti OR 'sipuleucel-t':ab,ti OR 'apc 8015':ab,ti
78	strontium:ab,ti
79	'tak-700':ab,ti OR 'tak 700':ab,ti OR 'tak700':ab,ti
80	triptorelin:ab,ti OR '6-d-tryptophan-lh-rh':ab,ti OR '6-d-tryptophanluteinizing hormone-releasing factor':ab,ti OR 'ay-25650':ab,ti OR 'cl-118,532':ab,ti OR 'decapeptyl':ab,ti OR detryptoreline:ab,ti OR '[d trp 6] lhrh':ab,ti OR 'arvekap':ab,ti OR 'ay 25650':ab,ti OR 'ay25650':ab,ti OR 'd trp 6 lhrh':ab,ti OR 'd trp 6 luteinizing hormone releasing hormone':ab,ti OR 'gonadorelin [6 dextro tryptophan]':ab,ti OR 'gonadotropin releasing hormone [6 dextro tryptophan]':ab,ti OR 'lhrh (d trp 6)':ab,ti OR 'lhrh [6 dextro tryptophan]':ab,ti OR 'luteinizing hormone releasing hormone [6 dextro tryptophan]':ab,ti OR trelstar:ab,ti OR 'trelstar la':ab,ti OR tryptorelin:ab,ti
81	'le 29060':ab,ti OR 'le29060':ab,ti OR 'leukoblastin':ab,ti OR rozevin:ab,ti OR 'vin blastine':ab,ti OR vinblastin*:ab,ti OR vincaleucoblastin*:ab,ti OR vincaleukoblastin*:ab,ti OR vincoblastin*:ab,ti OR vincoleucoblastin*:ab,ti OR vincoleukoblastin*:ab,ti OR vinleucoblastine:ab,ti OR vlb:ab,ti
82	navelbine:ab,ti OR vinorelbine:ab,ti OR '3,4-didehydro-4-deoxy-c-norvincaleukoblastine':ab,ti OR '5-nor-anhydrovinblastine':ab,ti OR dihydroxydeoxynorvinkaleukoblastine:ab,ti OR 'nor-5-anhydrovinblastine':ab,ti
83	zd4054:ab,ti OR 'zd 4054':ab,ti OR zibotentan:ab,ti OR 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide':ab,ti
84	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR reclast:ab,ti OR 'zol 446':ab,ti OR 'cgp 42446':ab,ti
85	'5, 6 dimethyl 9 oxo 9h xanthene 4 acetic acid':ab,ti OR dmxaa:ab,ti OR 'as 1404':ab,ti OR as1404:ab,ti OR 'asa 404':ab,ti OR asa404:ab,ti OR 'nsc 640488':ab,ti OR nsc640488:ab,ti
86	'imc a12':ab,ti OR 'imc ? a12':ab,ti OR cixutumumab:ab,ti OR 'anti-igf-1r recombinant monoclonal antibody imc-a12':ab,ti
87	patupilone:ab,ti OR 'epo 906':ab,ti OR epo906:ab,ti OR 'epothilon b':ab,ti
88	sunitinib:ab,ti OR 'pha 2909040ad':ab,ti OR pha2909040ad:ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR su011248:ab,ti OR su10398:ab,ti OR su11248:ab,ti OR sutent:ab,ti
89	'cab':ab,ti OR 'complete androgen blockade':ab,ti
90	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
91	#27 AND #35 AND #90
92	#27 AND #35 AND #90 AND [20-11-2012]/sd

Table 118: Embase and MEDLINE database search strategy (searched on 02.09.13)

#	Search string
1	'economics'/de
2	'economic aspect'/de
3	'cost'/de
4	'health care cost'/exp OR 'health care cost'
5	'drug cost'/de
6	'hospital cost'/de
7	'socioeconomics'/de
8	'health economics'/de
9	'pharmacoeconomics'/de
10	'fee'/exp
11	'budget'/exp
12	'economic evaluation'/exp
13	'hospital finance'/de OR 'financial management'/de
14	'health care financing'/de
15	'health care utilization'/de
16	'low cost'
17	'high cost'

#	Search string
18	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*
19	fiscal OR funding OR financial OR finance
20	cost NEXT/1 estimate*
21	'cost variable'
22	unit NEXT/1 cost*
23	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti
24	cost* NEAR/3 (treat* OR therap*)
25	health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization)
26	resource NEXT/1 (utilisation OR utilization OR use)
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
28	'prostate cancer'/exp
29	'prostate tumor'/de
30	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
31	crpc
32	castrat* NEAR/3 resistant
33	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
34	#32 AND #33
35	#28 OR #29 OR #30 OR #31 OR #34
36	'2,4-dioxo-5-fluoropyrimidine':ab,ti OR '5-fluoro-2,4(1h, 3h)-pyrimidinedione':ab,ti OR '5-fluorouracil':ab,ti OR '5-fluracil':ab,ti OR '5-fu':ab,ti OR accusite:ab,ti OR 'actino-hermal':ab,ti OR adrucil:ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efudex:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR 'fluoro uracil':ab,ti OR fluoroplex:ab,ti OR fluorouracil:ab,ti OR fluouracil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR 'ro 2-9757':ab,ti OR timazin:ab,ti
37	abarelix:ab,ti OR plenaxis:ab,ti OR 'ppi 149':ab,ti OR 'r 3827':ab,ti OR ppi149:ab,ti OR r3827:ab,ti
38	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti
39	aflibercept:ab,ti OR 'ave0005':ab,ti OR 'vascular endothelial growth factor trap':ab,ti OR 'vegf trap r1r2':ab,ti OR 'vegf trap':ab,ti OR 'vasculotropin trap':ab,ti
40	'2-(p-aminophenyl)-2-ethylglutarimide':ab,ti OR '3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione':ab,ti OR 'alpha-(4-aminophenyl)-alpha-ethylglutarimide':ab,ti OR aminoblastin:ab,ti OR aminoglutethimide:ab,ti OR 'ba-16038':ab,ti OR cytadren:ab,ti OR elipten:ab,ti OR mamomit:ab,ti OR orimenten*:ab,ti OR orimeten:ab,ti OR rodazol:ab,ti
41	'abt 627':ab,ti OR atrasentan:ab,ti OR xinlay:ab,ti OR abt627:ab,ti OR 'a 147627':ab,ti OR a147627:ab,ti OR a1277*:ab,ti OR (a NEXT/1 1277*):ab,ti
42	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'anti-vegf humanized monoclonal antibody':ab,ti OR 'anti-vegf rhumab':ab,ti OR 'recombinant humanized anti-vegf monoclonal antibody':ab,ti OR 'rhumab-vegf':ab,ti
43	bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR 'ici 176334':ab,ti OR ici176334:ab,ti OR raffolutil:ab,ti
44	'1-hydroxy-7beta,10beta-dimethoxy-9-oxo-5beta,20-epoxytax-11-ene-2alpha,4,13alpha-triyl 4-acetate 2-benzoate 13-[(2r,3s)-3-([(tertbutoxy)carbonyl]amino)-2-hydroxy-3-phenylpropanoate]':ab,ti OR cabazitaxel:ab,ti OR 'rpr 116258a':ab,ti OR 'taxoid xrp6258':ab,ti OR xrp6258:ab,ti
45	'(sp-4-2)-diammine[1,1-cyclobutanedicarboxylato(2--)-o,o]platinum':ab,ti OR '1,1-cyclobutanedicarboxylic acid platinum complex':ab,ti OR blastocarb:ab,ti OR carboplatin:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR cbdca:ab,ti OR 'cis-diammine(1,1-cyclobutanedicarboxylato) platinum(ii)':ab,ti OR displata:ab,ti OR ercar:ab,ti OR 'jm-8':ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR paraplat*:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti
46	'nsc 81340':ab,ti OR 'nsc 81430':ab,ti OR nsc81340:ab,ti OR nsc81430:ab,ti OR 'sh 714':ab,ti OR sh714:ab,ti OR sinovir:ab,ti OR virilit:ab,ti OR cyproterone:ab,ti
47	'corticosteroid'/exp
48	'antiandrogen'/exp
49	'gonadorelin agonist'/exp OR 'lhrh agonist'
50	'cancer immunotherapy'/exp
51	dasatinib:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti OR sprycel:ab,ti
52	degarelix:ab,ti OR fe200486:ab,ti OR 'fe 200486':ab,ti
53	dexamethasone:ab,ti OR 'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflog*:ab,ti OR arcodex*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR (dacort* NEAR/1 fue*):ab,ti OR dalalone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR decacort*:ab,ti OR dekacort*:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameto*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR d?xamethasone:ab,ti OR esacortene:ab,ti OR 'ex s1':ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR (fluor* NEAR/1 predniso*):ab,ti OR fluormethylpredniso*:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR dexa*:ab,ti OR hexadecad*:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isopto*:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazon*:ab,ti OR 'metisone lafi':ab,ti OR millicorten*:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR opticort*:ab,ti OR oradex*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR 'predni f tablinen':ab,ti OR 'prednisolone f':ab,ti OR prodex*:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti OR decadeltosona:ab,ti OR decadeltosone:ab,ti OR decadion*:ab,ti OR decadran:ab,ti OR decadron*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti

#	Search string
54	'(e)-4,4-(1,2-diethyl-1,2-ethenediyl)bisphenol':ab,ti OR '3, 4-bis(p-hydroxyphenyl)-3-hexene':ab,ti OR acnestrol:ab,ti OR 'alpha,alpha-diethylstilbenediol':ab,ti OR antigestil:ab,ti OR apstil:ab,ti OR boestrol:ab,ti OR bufon:ab,ti OR 'cyren a':ab,ti OR des:ab,ti OR diastyl:ab,ti OR diethylstilbenediol:ab,ti OR diethylstilbestrolum:ab,ti OR diethylstilbestrol:ab,ti OR diethylstilboestrol:ab,ti OR distilbene:ab,ti OR domestrol:ab,ti OR estrobene:ab,ti OR estromenin:ab,ti OR estrosyn:ab,ti OR fonatol:ab,ti OR grafestrol:ab,ti OR makarol:ab,ti OR microest:ab,ti OR milestrol:ab,ti OR 'neo-oestronol i':ab,ti OR oestrogeni*:ab,ti OR oestromenin:ab,ti OR oestromensyl:ab,ti OR oestromon:ab,ti OR sexocretin:ab,ti OR sibol:ab,ti OR stilbestro*:ab,ti OR stilbetin:ab,ti OR stilboefral:ab,ti OR stilboestrol:ab,ti OR stilkap:ab,ti OR synestrin:ab,ti OR synthoestrin:ab,ti OR vagestrol:ab,ti OR hexanestrol:ab,ti OR hexestrofen:ab,ti OR hexital:ab,ti OR hexron:ab,ti OR hexypheen:ab,ti OR 'hi bestrol':ab,ti OR 'hormoestrol':ab,ti OR menostilbene:ab,ti OR 'meso hexestrol':ab,ti OR mesohexestrol:ab,ti OR micrest:ab,ti OR 'neo estranol':ab,ti OR 'nsc 3070':ab,ti OR 'nsc 35752':ab,ti OR 'nsc 9894':ab,ti OR oekolp:ab,ti OR oestrostilben:ab,ti OR oestrosyntal:ab,ti OR orestrol:ab,ti OR ovendosyn:ab,ti OR pabestrol:ab,ti OR pabestrosalve:ab,ti OR palestrol:ab,ti OR proestrin:ab,ti OR serral:ab,ti
55	docetaxel:ab,ti OR taxotere:ab,ti
56	'(8s-cis)-10-[(3-amino-2,3,6-trideoxy-alpha-l-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione':ab,ti OR '14-hydroxydaunomycin':ab,ti OR doxorubicin:ab,ti OR 'hydroxyl daunorubicin':ab,ti OR adriablastin*:ab,ti OR adriacin:ab,ti OR adriam?cina:ab,ti OR adriamycin:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR dexorubicin:ab,ti OR 'dox sl':ab,ti OR doxil:ab,ti OR doxorubicin*:ab,ti OR 'fi 106':ab,ti OR lipodox:ab,ti OR 'liposomal doxorubicin':ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR 'pegylated liposomal doxorubicin':ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti
57	dutasteride:ab,ti OR 'gg 745':ab,ti OR 'gg745':ab,ti OR avodart:ab,ti OR avolve:ab,ti OR advodart:ab,ti OR duagen:ab,ti OR 'gi 198745':ab,ti OR gi198745*:ab,ti
58	e7389:ab,ti OR 'e 7389':ab,ti OR eribulin:ab,ti OR 'halichondrin b analog':ab,ti
59	estramustine:ab,ti OR 'leo 275':ab,ti OR 'leo 462':ab,ti OR 'nsc 89199':ab,ti OR 'ro 21 8837':ab,ti OR 'ro 22 2296 000':ab,ti OR leo275:ab,ti OR leo462:ab,ti OR nsc89199:ab,ti OR ro218837:ab,ti OR ro222296000:ab,ti
60	'4-demethylepipodophyllotoxin 9-[4,6-o-ethylidene-beta-d-glucopyranoside':ab,ti OR 'demethyl epipodophyllotoxin ethylidine glucoside':ab,ti OR epeg:ab,ti OR etoposide:ab,ti OR vepesid:ab,ti OR 'vp 16-213':ab,ti OR etomedac:ab,ti OR etopol:ab,ti OR lastet:ab,ti OR 'nk 171':ab,ti OR 'nsc 141540':ab,ti OR toposar:ab,ti OR vepesid*:ab,ti
61	'(5alpha,17beta)-n-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide':ab,ti OR 'chibro-proscar':ab,ti OR finasteride:ab,ti OR finastid:ab,ti OR 'mk 906':ab,ti OR 'pro-cure':ab,ti OR propecia:ab,ti OR propeshia:ab,ti OR proscar:ab,ti OR prostide:ab,ti OR urprosan:ab,ti OR 'ym 152':ab,ti
62	flutamide:ab,ti OR apimid:ab,ti OR chimax:ab,ti OR eulexine:ab,ti OR flucinome:ab,ti OR flucinom:ab,ti OR flugerel:ab,ti OR fluken:ab,ti OR flulem:ab,ti OR 'fluta-gry':ab,ti OR flutabene:ab,ti OR flutacan:ab,ti OR flutamex:ab,ti OR flutamin:ab,ti OR flutan:ab,ti OR flutaplex:ab,ti OR flut:ab,ti OR fugerel:ab,ti OR grisetin:ab,ti OR oncosal:ab,ti OR profamid:ab,ti OR prostacur:ab,ti OR prostadirex:ab,ti OR prostica:ab,ti OR prostogenat:ab,ti OR 'sch 13521':ab,ti OR sch13521:ab,ti OR tafenil:ab,ti OR tecnoflut:ab,ti OR testotard:ab,ti OR drogenil:ab,ti OR euflex:ab,ti OR eulexin:ab,ti OR flumid:ab,ti OR niftolid:ab,ti OR niphtholid:ab,ti OR sebatrol:ab,ti
63	goserelin:ab,ti OR 'ici-118630':ab,ti OR 'ici 118 630':ab,ti OR 'ici 118630':ab,ti OR ici118630:ab,ti OR zoladex:ab,ti
64	'(11beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione':ab,ti OR 'aeroseb-hc':ab,ti OR 'barseb hc':ab,ti OR cetacort:ab,ti OR 'cort-dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortifan:ab,ti OR cortisol:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR domolene:ab,ti OR eldecort:ab,ti OR hautosone:ab,ti OR 'heb-cort':ab,ti OR hydrocortisone:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR 'komed-hc':ab,ti OR nutracort:ab,ti OR proctocort:ab,ti OR rectoid:ab,ti OR therapeutic:ab,ti AND hydrocortisone:ab,ti OR alphaderm:ab,ti OR barseb:ab,ti OR cetacort:ab,ti OR cobadex:ab,ti OR 'compound f':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortibel:ab,ti OR cortifan:ab,ti OR cortifoam:ab,ti OR cortiment:ab,ti OR cortiphate:ab,ti OR cortisol*:ab,ti OR cortoderm:ab,ti OR cortril:ab,ti OR dermolate:ab,ti OR dioderm:ab,ti OR duomedihaler:ab,ti OR 'ef cortelan':ab,ti OR efcortelan:ab,ti OR egocort:ab,ti OR eksalb:ab,ti OR eldecort:ab,ti OR ficortril:ab,ti OR hebcort:ab,ti OR hycort:ab,ti OR hydracort:ab,ti OR hydrasson:ab,ti OR 'hydro ricortex':ab,ti OR hydrocort:ab,ti OR hydrocorticosteroid:ab,ti OR hydrocortisate:ab,ti OR hydrocortis*:ab,ti OR hydrocortone:ab,ti OR hydroderm:ab,ti OR hysone:ab,ti OR hytone:ab,ti OR incortin:ab,ti OR medihaler:ab,ti OR mildison:ab,ti OR munitren:ab,ti AND 'neo cortef':ab,ti OR neocortef:ab,ti OR novohydrocort:ab,ti OR 'nsc 10483':ab,ti OR 'nsc 741':ab,ti OR nutracort:ab,ti OR otosone:ab,ti OR penecort:ab,ti OR prepcort:ab,ti OR proctocort:ab,ti OR proctosone:ab,ti OR rectocort:ab,ti OR schericur:ab,ti OR 'scherosone f':ab,ti OR 'solu cortef':ab,ti OR synacort:ab,ti OR vasocort:ab,ti
65	'anti-cytotoxic t-lymphocyte-associated antigen-4 monoclonal antibody':ab,ti OR ipilimumab:ab,ti OR 'mdx-010':ab,ti OR 'mdx-ctla4':ab,ti OR 'bms 734016':ab,ti
66	jm216:ab,ti OR 'jm 216':ab,ti
67	ketoconazole:ab,ti OR fungarest:ab,ti OR fungoral:ab,ti OR ketoderm:ab,ti OR ketoisdin:ab,ti OR nizoral:ab,ti OR orifungal:ab,ti OR panfungol:ab,ti OR xolegel:ab,ti OR anisole:ab,ti OR cetonax:ab,ti OR 'dio 902':ab,ti OR dio902:ab,ti OR 'kw 1414':ab,ti OR kw1414:ab,ti OR micoral:ab,ti OR nisoral:ab,ti OR oxocanazole:ab,ti OR oxoconazole:ab,ti OR 'r 41 400':ab,ti OR r41400:ab,ti OR terzolin:ab,ti
68	leuprolide:ab,ti OR leuprorelin:ab,ti OR leuplin:ab,ti OR leupro*:ab,ti OR lucrin:ab,ti OR lupride:ab,ti OR lupron:ab,ti OR procrin:ab,ti OR prostap:ab,ti OR tap144:ab,ti OR 'tap 144':ab,ti
69	mdv3100:ab,ti OR 'mdv3100':ab,ti
70	megastrol:ab,ti
71	mitoxantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mito?antrone:ab,ti OR novanthron:ab,ti OR novantron*:ab,ti OR 'now 85 34':ab,ti OR 'now 8534':ab,ti OR now8534:ab,ti OR 'nsc 279836':ab,ti OR 'nsc 301739':ab,ti OR 'nsc 301739d':ab,ti OR nsc279836:ab,ti OR nsc301739:ab,ti OR nsc301739d:ab,ti
72	nilutamide:ab,ti OR anandron:ab,ti OR nilandron:ab,ti OR anadron:ab,ti OR nitulamide:ab,ti OR 'rn 23908':ab,ti OR 'ru 23908':ab,ti OR rn23908:ab,ti OR ru23908:ab,ti
73	'abi 007':ab,ti OR 'abi007':ab,ti OR abraxane:ab,ti OR 'bms 181339':ab,ti OR coroxane:ab,ti OR genexol:ab,ti OR hunxol:ab,ti OR intaxel:ab,ti OR 'nsc 125973':ab,ti OR paxceed:ab,ti OR paclitaxel:ab,ti OR paxene:ab,ti OR taxol:ab,ti OR yewtaxan:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti

#	Search string
74	'pamidronic acid':ab,ti OR pamidronate:ab,ti OR aredia:ab,ti OR aminomux:ab,ti OR 'gcp-23339a':ab,ti
75	prednison*:ab,ti OR prednisolon*:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR 'de cortin':ab,ti OR decortin:ab,ti OR 'de cortisyl':ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR 'delta(1)-cortisone':ab,ti OR 'delta-dome':ab,ti OR deltacortene:ab,ti OR deltacortisone:ab,ti OR deltadehydrocortisone:ab,ti OR deltasone:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR lisacort:ab,ti OR 'meprosona-f':ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR 'panasol-s':ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicorten:ab,ti OR predicor:ab,ti OR 'prednicen-m':ab,ti OR prednicort:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednisone:ab,ti OR prednisonum:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti OR 'sk-prednisone':ab,ti OR sterapred:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR decortancyl:ab,ti OR dekortin:ab,ti OR delitisone:ab,ti OR 'delta cortelan':ab,ti OR 'delta cortisone':ab,ti OR 'delta dome':ab,ti OR 'delta e':ab,ti OR 'delta prenovis':ab,ti OR deltacorten:ab,ti OR deltacortone:ab,ti OR 'di adreson':ab,ti OR diadreson:ab,ti OR encorton*:ab,ti OR enkorton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone:ab,ti OR orisane:ab,ti OR precort:ab,ti OR precortal:ab,ti OR pronison*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti
76	samarium:ab,ti
77	sipuleucelt:ab,ti OR 'apc8015 vaccine':ab,ti OR 'apc8015':ab,ti OR 'pa2024 (pap/gm-csf)-loaded dendritic cell vaccine':ab,ti OR provenge:ab,ti OR 'sipuleucel-t':ab,ti OR 'apc 8015':ab,ti
78	strontium:ab,ti
79	'tak-700':ab,ti OR 'tak 700':ab,ti OR 'tak700':ab,ti
80	triptorelin:ab,ti OR '6-d-tryptophan-lh-rh':ab,ti OR '6-d-tryptophanluteinizing hormone-releasing factor':ab,ti OR 'ay-25650':ab,ti OR 'cl-118,532':ab,ti OR 'decapeptyl':ab,ti OR detryptoreline:ab,ti OR '[d trp 6] lhrh':ab,ti OR 'arvekap':ab,ti OR 'ay 25650':ab,ti OR 'ay25650':ab,ti OR 'd trp 6 lhrh':ab,ti OR 'd trp 6 luteinizing hormone releasing hormone':ab,ti OR 'gonadorelin [6 dextro tryptophan]':ab,ti OR 'gonadotropin releasing hormone [6 dextro tryptophan]':ab,ti OR 'lhrh (d trp 6)':ab,ti OR 'lhrh [6 dextro tryptophan]':ab,ti OR 'luteinizing hormone releasing hormone [6 dextro tryptophan]':ab,ti OR trelstar:ab,ti OR 'trelstar la':ab,ti OR tryptorelin:ab,ti
81	'le 29060':ab,ti OR 'le29060':ab,ti OR 'leukoblastin':ab,ti OR rozevin:ab,ti OR 'vin blastine':ab,ti OR vinblastin*:ab,ti OR vincaleucoblastin*:ab,ti OR vincaleukoblastin*:ab,ti OR vincoblastin*:ab,ti OR vincoleucoblastin*:ab,ti OR vincoleukoblastin*:ab,ti OR vinleucoblastine:ab,ti OR vlb:ab,ti
82	navelbine:ab,ti OR vinorelbine:ab,ti OR '3,4-didehydro-4-deoxy-c-norvincaleukoblastine':ab,ti OR '5-nor-anhydrovinblastine':ab,ti OR dihydroxydeoxynorvinkaleukoblastine:ab,ti OR 'nor-5-anhydrovinblastine':ab,ti
83	zd4054:ab,ti OR 'zd 4054':ab,ti OR zibotentan:ab,ti OR 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide':ab,ti
84	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR reclast:ab,ti OR 'zol 446':ab,ti OR 'cgp 42446':ab,ti
85	'5, 6 dimethyl 9 oxo 9h xanthene 4 acetic acid':ab,ti OR dmxaa:ab,ti OR 'as 1404':ab,ti OR as1404:ab,ti OR 'asa 404':ab,ti OR asa404:ab,ti OR 'nsc 640488':ab,ti OR nsc640488:ab,ti
86	'imc a12':ab,ti OR 'imc ? a12':ab,ti OR cixutumumab:ab,ti OR 'anti-igf-1r recombinant monoclonal antibody imc-a12':ab,ti
87	patupilone:ab,ti OR 'epo 906':ab,ti OR epo906:ab,ti OR 'epothilon b':ab,ti
88	sunitinib:ab,ti OR 'pha 2909040ad':ab,ti OR pha2909040ad:ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR su011248:ab,ti OR su10398:ab,ti OR su11248:ab,ti OR sutent:ab,ti
89	'cab':ab,ti OR 'complete androgen blockade':ab,ti
90	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
91	#27 AND #35 AND #90
92	#27 AND #35 AND #90 AND [30-5-2013]/sd

Table 119: Cochrane database search strategy (searched on 20.11.12)

#	Search string
1	MeSH descriptor Prostatic Neoplasms explode all trees
2	prostate tumor
3	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
4	crpc
5	castrat* NEAR/3 resistant
6	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
7	(#5 AND #6)
8	(#1 OR #2 OR #3 OR #4 OR #7)
9	('5-Fluorouracil' OR '5-Fluracil' OR '5-FU' OR AccuSite OR 'Actino-Hermal' OR Adrucil OR Arumel OR Cytosafe OR Efudex OR Efurix OR Fiverocil OR 'Fluoro Uracil' OR Fluoroplex OR Fluorouracil OR Fluouracil OR Flurablastin OR Fluracedyl OR Fluracil OR Fluril OR Fluroblastin OR Flurox OR Ribofluor OR 'Ro 2-9757' OR Timazin):ab,ti,kw
10	(Abarelix OR Plenaxis OR 'PPI 149' OR 'R 3827' OR PPI149 OR R3827):ab,ti,kw
11	(Abiraterone OR 'cb 7598' OR cb7598):ab,ti,kw
12	(Aflibercept OR 'AVE0005' OR 'Vascular Endothelial Growth Factor Trap' OR 'VEGF Trap R1R2' OR 'VEGF Trap' OR 'vasculotropin trap'):ab,ti,kw
13	(Aminoblastin OR Aminoglutethimide OR 'BA-16038' OR 'Ba-16038' OR Cytadren OR Elipten OR Mamomit OR Orimenten* OR Orimeten OR Rodazol):ab,ti,kw
14	('abt 627' or atrasentan or xinlay or abt627 or 'a 147627' or a147627 or a1277* or a NEXT/1 1277*):ab,ti,kw

#	Search string
15	(Bevacizumab OR avastin OR 'nsc 704865' OR nsc704865 OR 'anti-vegf' OR 'Anti-VEGF Humanized Monoclonal Antibody' OR 'Anti-VEGF rhuMAb' OR 'Recombinant Humanized Anti-VEGF Monoclonal Antibody' Or 'rhuMab-VEGF'):ab,ti,kw
16	(Bicalutamide OR Casodex OR Cosudex OR 'ICI 176334' OR ICI176334 OR raffolutil):ab,ti,kw
17	(Cabazitaxel OR RPR-116258A OR 'Taxoid XRP6258' OR XRP6258):ab,ti,kw
18	(Blastocarb OR Carboplatin OR Carboplat* OR Carbosin OR Carbosol OR Carbotec OR CBDCA OR Displata OR Ercar OR 'JM-8' OR Nealorin OR Novoplatinum OR Paraplat* OR Platinwas OR Ribocarbo):ab,ti,kw
19	('nsc 81340' OR 'nsc 81430' OR nsc81340 OR nsc81430 OR 'sh 714' OR sh714 OR sinovir OR virilit OR cyproterone):ab,ti,kw
20	(dasatinib OR 'bms 354825' OR bms354825 OR sprycel):ab,ti,kw
21	(Degarelix OR FE200486 OR 'FE 200486'):ab,ti,kw
22	(dexamethasone OR 'aeroseb dex' OR aflucoson* OR anaflog* OR arcodex* OR azium OR calonat OR cebedex OR colofoam OR cortidron* OR cortisumman OR (dacort* NEAR/1 fue*) OR dalalone OR decilone OR decofluor OR dectancyl OR decacort* OR dekacort* OR delladec OR deltafluoren OR dergramin OR deronil OR desadrene OR desalark OR desameto* OR dexa* OR dexinoral OR dexionil OR dexone OR dextelan OR dezone OR d?xamethasone OR esacortene OR 'ex s1' OR exadion* OR firmalone OR (fluor* NEAR/1 predniso*) OR fluormethylpredniso* OR fluormone OR fluorocort OR fluorodelta OR fortecortin OR gammacorten* OR grosodexon* OR dexa* OR hexadecad* OR hexadiol OR hexadrol OR isnacort OR isopto* OR 'lokalison f' OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson* OR metasolon* OR methazon* OR 'metisone lafi' OR millicorten* OR nisomethasona OR novocort OR opticort* OR oradex* OR orgadrone OR policort OR posurdex OR 'predni f tablinen' OR 'prednisolone f' OR prodex* OR sanamethasone OR spoloven OR triamcimetil OR visumethazone OR decadeltosona OR decadeltosone OR decadion* OR decadran OR decadron* OR decaesadril OR decamethasone OR decasone OR decaspray OR decasterolone):ab,ti,kw
23	(Acnestrol OR 'Alpha,alpha-diethylstilbenediol' OR Antigestil OR Apstil OR Boestrol OR Bufon OR 'Cyren A' OR DES OR Diastyl OR Diethylstilbenediol OR Diethylstilbestrolum OR diethylstilbestrol OR Diethylstilboestrol OR Distilbene OR Domestrol OR Estrobene OR Estromenin OR Estrosyn OR Fonatol OR Grafestrol OR Makarol OR Microest OR Milestrol OR 'Neo-Oestronol I' OR Oestrogeni* OR Oestromenin OR Oestromensyl OR Oestromon OR Palestrol OR Serral OR Sexocretin OR Sibol OR Stilbestro* OR Stilbetin OR Stilboefral OR Stilboestrol OR Stilkap OR Synestrin OR Synthoestrin OR Vagestrol OR Vagestrol OR Hexanestrol OR hexestrofen OR hexital OR hexron OR hexypheen OR 'hi bestrol' OR 'hormoestrol' OR menostilbene OR 'meso hexestrol' OR mesohexestrol OR micrest OR 'neo estranol' OR 'nsc 3070' OR 'nsc 35752' OR 'nsc 9894' OR oekolp OR oestrostilben OR oestrosyntal OR orestrol OR ovendosyn OR pabestrol OR pabestrosalve OR palestrol OR proestrin OR serral):ab,ti,kw
24	(Docetaxel OR Taxotere):ab,ti,kw
25	(doxorubicin OR 'Hydroxyl Daunorubicin' OR adriablastin* OR adriacin OR adriam?cina OR adriamycin OR adriblastin* OR caelyx OR dexorubicin OR 'dox sl' OR doxil OR doxorubicin* OR 'fi 106' OR lipodox OR 'liposomal doxorubicin' OR myocet OR 'nsc 123127' OR 'pegylated liposomal doxorubicin' OR rastocin OR resmycin OR 'rp 25253' OR rubex OR sarcodoxome OR 'tlc d 99'):ab,ti,kw
26	(Dutasteride OR 'GG 745' OR 'GG745' OR Avodart OR Avolve OR advodart OR duagen OR 'gi 198745' or gi198745*):ab,ti,kw
27	(e7389 or 'e 7389' or eribulin or 'halichondrin b analog'):ab,ti,kw
28	(Estramustine OR 'Leo 275' OR 'RO 21 8837' OR 'leo 462' OR 'nsc 89199' OR 'ro 21 8837' OR 'ro 22 2296 000' OR Leo275 OR RO218837 OR Leo462 OR nsc89199 OR ro218837 OR ro222296000):ab,ti,kw
29	(EPEG OR Etoposide OR Lastet OR Vepesid OR 'VP 16-213' OR etomedac OR etopol OR lastet OR 'nk 171' OR 'nsc 141540' OR toposar OR vepesid*):ab,ti,kw
30	('Chibro-Proscar' OR Finasteride OR Finastid OR 'MK 906' OR 'Pro-Cure' OR Propecia OR Propeshia OR Proscar OR Prostide OR Urprosan OR 'ym 152'):ab,ti,kw
31	(Flutamide OR Apimid OR Chimax OR Drogenil OR Euflex OR Eulexine OR Eulexin OR Flucinome OR Flucinom OR Flugerel OR Fluken OR Flulem OR 'Fluta-Gry' OR Flutabene OR Flutacan OR Flutamex OR Flutamin OR Flutan OR Flutaplex OR FLUT OR Fugerel OR Grisetin OR Niftolid OR Oncosal OR Profamid OR Prostacur OR Prostadirex OR Prostica OR Prostogenat OR 'SCH 13521' OR Sch13521 OR Tafenil OR Tecnoflut OR Testotard OR drogenil OR euflex OR eulexin OR flumid OR niftolid OR niphtholid OR sebatrol):ab,ti,kw
32	(Goserelin OR 'ICI-118630' OR 'ici 118 630' OR 'ici 118630' OR ici118630 OR zoladex):ab,ti,kw
33	('Aeroseb-HC' OR 'Barseb HC' OR Cetacort OR 'Cort-Dome' OR Cortef OR Cortenema OR Cortifan OR Cortisol OR Cortispray OR Cortril OR Dermacort OR Domolene OR Eldecort OR Hautosone OR 'Heb-Cort' OR Hydrocortisone OR Hydrocortone OR Hytone OR 'Komed-HC' OR Nutracort OR Proctocort OR Rectoid OR Therapeutic Hydrocortisone OR alphaderm OR barseb OR cetacort OR cobadex OR 'compound f' OR cortef OR cortenema OR cortibel OR cortifan OR cortifoam OR cortiment OR cortiphate OR cortisol* OR cortoderm OR cortril OR dermolate OR dioderm OR duomedihaler OR 'ef cortelan' OR efcortelan OR egocort OR eksalb OR eldecort OR ficortril OR hebcort OR hycort OR hydracort OR hydrasson OR 'hydro ricortex' OR hydrocort OR hydrocorticosteroid OR hydrocortisate OR hydrocortis* OR hydrocortone OR hydroderm OR hysone OR hytone OR incortin OR medihaler OR mildison OR munitren 'neo cortef' OR neocortef OR novohydrocort OR 'nsc 10483' OR 'nsc 741' OR nutracort OR otosone OR penecort OR prepcort OR proctocort OR proctosone OR rectocort OR schericur OR 'scherosone f' OR 'solu cortef' OR synacort OR vasocort):ab,ti,kw
34	('Anti-Cytotoxic T-Lymphocyte-Associated Antigen-4 Monoclonal Antibody' OR Ipilimumab OR 'MDX-010' OR 'MDX-CTLA4' OR 'bms 734016'):ab,ti,kw
35	(JM216 OR 'JM 216'):ab,ti,kw
36	(Ketoconazole OR Fungarest OR Fungoral OR Ketoderm OR Ketoisdin OR Nizoral OR Orifungal OR Panfungol OR Xolegel OR Anisole OR cetonax OR 'dio 902' OR dio902 OR 'kw 1414' OR kw1414 OR micoral OR nisoral OR oxocanazole OR oxoconazole OR 'r 41 400' OR r41400 OR terzolin):ab,ti,kw
37	(leuprolide or leuprorelin or leuplin or leupro* OR lucrin OR lupride OR lupron OR procrin OR prostap OR tap144 or 'tap 144'):ab,ti,kw
38	(Mdv3100 OR 'mdv3100'):ab,ti,kw

#	Search string
39	(megestrol):ab,ti,kw
40	(Mitoxantrone OR Dihydroxyanthracenedione OR Mito?antrone OR novanthron OR novantron* OR 'now 85 34' OR 'now 8534' OR now8534 OR 'nsc 279836' OR 'nsc 301739' OR 'nsc 301739d' OR nsc279836 OR nsc301739 OR nsc301739d):ab,ti,kw
41	(Nilutamide OR Anandron OR Nilandron OR anadron OR nitulamide OR 'rn 23908' OR 'ru 23908' OR rn23908 OR ru23908):ab,ti,kw
42	('abi 007' OR 'abi007' OR abraxane OR anzatax OR 'bms 181339' OR coroxane OR genexol OR hunxol OR intaxel OR 'nsc 125973' OR paxceed OR paclitaxel OR paxene OR taxol OR yewtaxan OR Anzatax OR Asotax OR Bristaxol OR Praxel):ab,ti,kw
43	('pamidronic acid' OR pamidronate OR aredia OR aminomux OR 'gcp-23339a'):ab,ti,kw
44	(prednison* OR prednisolon* OR Adasone OR Cortancyl OR Dacortin OR Dacortin OR 'De Cortin' OR DeCortin OR 'De cortisyl ' OR Decortisyl OR Decorton OR Decorton OR 'Delta-Cortisone' OR ' Delta-Dome' OR 'Delta-Dome' OR Deltacortene OR Deltacortisone OR Deltacortisone OR Deltadehydrocortisone OR Deltasone OR Deltasone OR Deltison OR Deltison OR Deltra OR Econosone OR Lisacort OR 'Meprosona-F' OR Metacortandracin OR Metacortandracin OR Meticorten OR Meticorten OR Ofisolona OR Orasone OR Orasone OR Panafcort OR 'Panasol-S' OR Paracort OR Predeltin OR Predicorten OR Predicor OR 'Prednicen-M' OR Prednicort OR Prednidib OR Prednilonga OR Prednilonga OR Predniment OR Prednisone OR Prednisonum OR Prednitone OR Promifen OR Servisone OR Servisone OR 'Sk-Prednisone' OR Sterapred):ab,ti,kw
45	Samarium:ab,ti,kw
46	(Sipuleucelt OR 'APC8015 Vaccine' OR 'APC8015' OR 'PA2024 Loaded Dendritic Cell Vaccine' OR Provenge OR 'Sipuleucel-T' OR 'apc 8015'):ab,ti,kw
47	Strontium:ab,ti,kw
48	('Tak-700' OR 'Tak 700' OR 'Tak700'):ab,ti,kw
49	(Triptorelin OR '6-D-Tryptophan-LH-RH' OR '6-D-Tryptophanluteinizing Hormone-releasing Factor' OR ' AY-25650' OR 'CL-118,532' OR 'Decapeptyl' OR Detryptoreline OR 'd trp 6 lhrh' OR 'arvekap' OR 'ay 25650' OR 'ay25650' OR 'd trp 6 lhrh' OR 'd trp 6 luteinizing hormone releasing hormone' OR 'gonadorelin 6 dextro tryptophan' OR 'gonadotropin releasing hormone 6 dextro tryptophan' OR 'lhrh d trp 6' OR 'lhrh 6 dextro tryptophan' OR 'luteinizing hormone releasing hormone 6 dextro tryptophan' OR trelstar OR 'trelstar la' OR tryptorelin):ab,ti,kw
50	('le 29060' OR 'le29060' OR 'leukoblastin' OR rozevin OR 'vin blastine' OR vinblastin* OR vincaleucoblastin* OR vincaleukoblastin* OR vincoblastin* OR vincoleucoblastin* OR vincoleukoblastin* OR vinleucoblastine OR vlb):ab,ti,kw
51	(Navelbine OR vinorelbine OR '3,4-Didehydro-4-deoxy-C-norvincaleukoblastine' OR '5-Nor-Anhydrovinblastine' OR Dihydroxydeoxynorvinkaleukoblastine OR 'nor-5-Anhydrovinblastine'):ab,ti,kw
52	(zd4054 or 'zd 4054' or zibotentan or 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide'):ab,ti,kw
53	('zoledronic acid' OR zoledronate OR zometa OR reclast OR 'zol 446' OR 'cgp 42446'):ab,ti,kw
54	(AS1404 OR 'AS 1404' OR DMXAA OR 'as 1404' OR as1404 OR 'asa 404' OR asa404 OR 'nsc 640488' OR nsc640488):ab,ti,kw
55	(IMC-A12 OR Cixutumumab OR 'Anti-IGF-1R Recombinant Monoclonal Antibody IMC-A12'):ab,ti,kw
56	(patupilone OR 'epo 906' OR epo906 OR 'epothilon b'):ab,ti,kw
57	(Sunitinib OR 'pha 2909040ad' OR pha2909040ad OR 'su 010398' OR 'su 011248' OR 'su 10398' OR 'su 11248' OR su010398 OR su011248 OR su10398 OR su11248 OR sutent):ab,ti
58	('cab' OR 'complete androgen blockade'):ab,ti,kw
59	MeSH descriptor Adrenal Cortex Hormones explode all trees
60	MeSH descriptor Androgen Antagonists explode all trees
61	MeSH descriptor Gonadotropin-Releasing Hormone explode all trees
62	cancer immunotherapy
63	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62)
64	(#8 AND #63), Limited to 2009 to 2011, Economic and HTA filter

Table 120: Cochrane database search strategy (searched on 30.05.13)

#	Search string
1	MeSH descriptor Prostatic Neoplasms explode all trees
2	prostate tumor
3	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
4	crpc
5	castrat* NEAR/3 resistant
6	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
7	(#5 AND #6)
8	(#1 OR #2 OR #3 OR #4 OR #7)
9	('5-Fluorouracil' OR '5-Fluracil' OR '5-FU' OR AccuSite OR 'Actino-Hermal' OR Adrucil OR Arumel OR Cytosafe OR Efudex OR Efurix OR Fiverocil OR 'Fluoro Uracil' OR Fluoroplex OR Fluorouracil OR Fluouracil OR Flurablastin OR Fluracedyl OR Fluracil OR Fluril OR Fluroblastin OR Flurox OR Ribofluor OR 'Ro 2-9757' OR Timazin):ab,ti,kw
10	(Abarelix OR Plenaxis OR 'PPI 149' OR 'R 3827' OR PPI149 OR R3827):ab,ti,kw
11	(Abiraterone OR 'cb 7598' OR cb7598):ab,ti,kw
12	(Aflibercept OR 'AVE0005' OR 'Vascular Endothelial Growth Factor Trap' OR 'VEGF Trap R1R2' OR 'VEGF Trap' OR 'vasculotropin trap'):ab,ti,kw

#	Search string
13	(Aminoblastin OR Aminoglutethimide OR 'BA-16038' OR 'Ba-16038' OR Cytadren OR Elipten OR Mamomit OR Orimenten* OR Orimeten OR Rodazol):ab,ti,kw
14	('abt 627' or atrasentan or xinlay or abt627 or 'a 147627' or a147627 or a1277* or a NEXT/1 1277*):ab,ti,kw
15	(Bevacizumab OR avastin OR 'nsc 704865' OR nsc704865 OR 'anti-vegf' OR 'Anti-VEGF Humanized Monoclonal Antibody' OR 'Anti-VEGF rhuMAb' OR 'Recombinant Humanized Anti-VEGF Monoclonal Antibody' Or 'rhuMab-VEGF'):ab,ti,kw
16	(Bicalutamide OR Casodex OR Cosudex OR 'ICI 176334' OR ICI176334 OR raffolutil):ab,ti,kw
17	(Cabazitaxel OR RPR-116258A OR 'Taxoid XRP6258' OR XRP6258):ab,ti,kw
18	(Blastocarb OR Carboplatin OR Carboplat* OR Carbosin OR Carbosol OR Carbotec OR CBDCA OR Displata OR Ercar OR 'JM-8' OR Nealorin OR Novoplatinum OR Paraplat* OR Platinwas OR Ribocarbo):ab,ti,kw
19	('nsc 81340' OR 'nsc 81430' OR nsc81340 OR nsc81430 OR 'sh 714' OR sh714 OR sinovir OR virilit OR cyproterone):ab,ti,kw
20	(dasatinib OR 'bms 354825' OR bms354825 OR sprycel):ab,ti,kw
21	(Degarelix OR FE200486 OR 'FE 200486'):ab,ti,kw
22	(dexamethasone OR 'aeroseb dex' OR aflucoson* OR anaflog* OR arcodex* OR azium OR calonat OR cebedex OR colofoam OR cortidron* OR cortisumman OR (dacort* NEAR/1 fue*) OR dalalone OR decilone OR decofluor OR dectancyl OR decacort* OR dekacort* OR delladec OR deltafluoren OR dergramin OR deronil OR desadrene OR desalark OR desameto* OR dexa* OR dexinoral OR dexionil OR dexone OR dextelan OR dezone OR d?xamethasone OR esacortene OR 'ex s1' OR exadion* OR firmalone OR (fluor* NEAR/1 predniso*) OR fluormethylpredniso* OR fluormone OR fluorocort OR fluorodelta OR fortecortin OR gammacorten* OR grosodexon* OR dexa* OR hexadecad* OR hexadiol OR hexadrol OR isnacort OR isopto* OR 'lokalison f' OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson* OR metasolon* OR methazon* OR 'metisone lafi' OR millicorten* OR nisomethasona OR novocort OR opticort* OR oradex* OR orgadrone OR policort OR posurdex OR 'predni f tablinen' OR 'prednisolone f' OR prodex* OR sanamethasone OR spoloven OR triamcimetil OR visumethazone OR decadeltosona OR decadeltosone OR decadion* OR decadran OR decadron* OR decaesadril OR decamethasone OR decasone OR decaspray OR decasterolone):ab,ti,kw
23	(Acnestrol OR 'Alpha,alpha-diethylstilbenediol' OR Antigestil OR Apstil OR Boestrol OR Bufon OR 'Cyren A' OR DES OR Diastyl OR Diethylstilbenediol OR Diethylstilbestrolum OR diethylstilbestrol OR Diethylstilboestrol OR Distilbene OR Domestrol OR Estrobene OR Estromenin OR Estrosyn OR Fonatol OR Grafestrol OR Makarol OR Microest OR Milestrol OR 'Neo-Oestronol I' OR Oestrogeni* OR Oestromenin OR Oestromensyl OR Oestromon OR Palestrol OR Serral OR Sexocretin OR Sibol OR Stilbestro* OR Stilbetin OR Stilboefral OR Stilboestrol OR Stilkap OR Synestrin OR Synthoestrin OR Vagestrol OR Vagestrol OR Hexanestrol OR hexestrofen OR hexital OR hexron OR hexypheen OR 'hi bestrol' OR 'hormoestrol' OR menostilbene OR 'meso hexestrol' OR mesohexestrol OR micrest OR 'neo estranol' OR 'nsc 3070' OR 'nsc 35752' OR 'nsc 9894' OR oekolp OR oestrostilben OR oestrosyntal OR orestrol OR ovendosyn OR pabestrol OR pabestrosalve OR palestrol OR proestrin OR serral):ab,ti,kw
24	(Docetaxel OR Taxotere):ab,ti,kw
25	(doxorubicin OR 'Hydroxyl Daunorubicin' OR adriablastin* OR adriacin OR adriam?cina OR adriamycin OR adriblastin* OR caelyx OR dexorubicin OR 'dox sl' OR doxil OR doxorubicin* OR 'fi 106' OR lipodox OR 'liposomal doxorubicin' OR myocet OR 'nsc 123127' OR 'pegylated liposomal doxorubicin' OR rastocin OR resmycin OR 'rp 25253' OR rubex OR sarcodoxome OR 'tlc d 99'):ab,ti,kw
26	(Dutasteride OR 'GG 745' OR 'GG745' OR Avodart OR Avolve OR advodart OR duagen OR 'gi 198745' or gi198745*):ab,ti,kw
27	(e7389 or 'e 7389' or eribulin or 'halichondrin b analog'):ab,ti,kw
28	(Estramustine OR 'Leo 275' OR 'RO 21 8837' OR 'leo 462' OR 'nsc 89199' OR 'ro 21 8837' OR 'ro 22 2296 000' OR Leo275 OR RO218837 OR Leo462 OR nsc89199 OR ro218837 OR ro222296000):ab,ti,kw
29	(EPEG OR Etoposide OR Lastet OR Vepesid OR 'VP 16-213' OR etomedac OR etopol OR lastet OR 'nk 171' OR 'nsc 141540' OR toposar OR vepesid*):ab,ti,kw
30	('Chibro-Proscar' OR Finasteride OR Finastid OR 'MK 906' OR 'Pro-Cure' OR Propecia OR Propeshia OR Proscar OR Prostide OR Urprosan OR 'ym 152'):ab,ti,kw
31	(Flutamide OR Apimid OR Chimax OR Drogenil OR Euflex OR Eulexine OR Eulexin OR Flucinome OR Flucinom OR Flugerel OR Fluken OR Flulem OR 'Fluta-Gry' OR Flutabene OR Flutacan OR Flutamex OR Flutamin OR Flutan OR Flutaplex OR FLUT OR Fugerel OR Grisetin OR Niftolid OR Oncosal OR Profamid OR Prostacur OR Prostadirex OR Prostica OR Prostogenat OR 'SCH 13521' OR Sch13521 OR Tafenil OR Tecnoflut OR Testotard OR drogenil OR euflex OR eulexin OR flumid OR niftolid OR niphtholid OR sebatrol):ab,ti,kw
32	(Goserelin OR 'ICI-118630' OR 'ici 118 630' OR 'ici 118630' OR ici118630 OR zoladex):ab,ti,kw
33	('Aeroseb-HC' OR 'Barseb HC' OR Cetacort OR 'Cort-Dome' OR Cortef OR Cortenema OR Cortifan OR Cortisol OR Cortispray OR Cortril OR Dermacort OR Domolene OR Eldecort OR Hautosone OR 'Heb-Cort' OR Hydrocortisone OR Hydrocortone OR Hytone OR 'Komed-HC' OR Nutracort OR Proctocort OR Rectoid OR Therapeutic Hydrocortisone OR alphaderm OR barseb OR cetacort OR cobadex OR 'compound f' OR cortef OR cortenema OR cortibel OR cortifan OR cortifoam OR cortiment OR cortiphate OR cortisol* OR cortoderm OR cortril OR dermolate OR dioderm OR duomedihaler OR 'ef cortelan' OR efcortelan OR egocort OR eksalb OR eldecort OR ficortril OR hebcort OR hycort OR hydracort OR hydrasson OR 'hydro ricortex' OR hydrocort OR hydrocorticosteroid OR hydrocortisate OR hydrocortis* OR hydrocortone OR hydroderm OR hysone OR hytone OR incortin OR medihaler OR mildison OR munitren 'neo cortef' OR neocortef OR novohydrocort OR 'nsc 10483' OR 'nsc 741' OR nutracort OR otosone OR penecort OR prepcort OR proctocort OR proctosone OR rectocort OR schericur OR 'scherosone f' OR 'solu cortef' OR synacort OR vasocort):ab,ti,kw
34	('Anti-Cytotoxic T-Lymphocyte-Associated Antigen-4 Monoclonal Antibody' OR Ipilimumab OR 'MDX-010' OR 'MDX-CTLA4' OR 'bms 734016'):ab,ti,kw
35	(JM216 OR 'JM 216'):ab,ti,kw
36	(Ketoconazole OR Fungarest OR Fungoral OR Ketoderm OR Ketoisdin OR Nizoral OR Orifungal OR Panfungol OR Xolegel OR Anisole OR cetonax OR 'dio 902' OR dio902 OR 'kw 1414' OR kw1414 OR micoral OR nisoral OR oxocanazole OR oxoconazole OR 'r 41 400' OR r41400 OR terzolin):ab,ti,kw

#	Search string
37	(leuprolide or leuprorelin or leuplin or leupro* OR lucrin OR lupride OR lupron OR procrin OR prostap OR tap144 or 'tap 144'):ab,ti,kw
38	(Mdv3100 OR 'mdv3100'):ab,ti,kw
39	(megestrol):ab,ti,kw
40	(Mitoxantrone OR Dihydroxyanthracenedione OR Mito?antrone OR novanthron OR novantron* OR 'now 85 34' OR 'now 8534' OR now8534 OR 'nsc 279836' OR 'nsc 301739' OR 'nsc 301739d' OR nsc279836 OR nsc301739 OR nsc301739d):ab,ti,kw
41	(Nilutamide OR Anandron OR Nilandron OR anadron OR nitulamide OR 'rn 23908' OR 'ru 23908' OR rn23908 OR ru23908):ab,ti,kw
42	('abi 007' OR 'abi007' OR abraxane OR anzatax OR 'bms 181339' OR coroxane OR genexol OR hunxol OR intaxel OR 'nsc 125973' OR paxceed OR paclitaxel OR paxene OR taxol OR yewtaxan OR Anzatax OR Asotax OR Bristaxol OR Praxel):ab,ti,kw
43	('pamidronic acid' OR pamidronate OR aredia OR aminomux OR 'gcp-23339a'):ab,ti,kw
44	(prednison* OR prednisolon* OR Adasone OR Cortancyl OR Dacortin OR Dacortin OR 'De Cortin' OR DeCortin OR 'De cortisyl ' OR Decortisyl OR Decorton OR Decorton OR 'Delta-Cortisone' OR ' Delta-Dome' OR 'Delta-Dome' OR Deltacortene OR Deltacortisone OR Deltacortisone OR Deltadehydrocortisone OR Deltasone OR Deltasone OR Deltison OR Deltison OR Deltra OR Econosone OR Lisacort OR 'Meprosona-F' OR Metacortandracin OR Metacortandracin OR Meticorten OR Meticorten OR Ofisolona OR Orasone OR Orasone OR Panafcort OR 'Panasol-S' OR Paracort OR Predeltin OR Predicorten OR Predicor OR 'Prednicen-M' OR Prednicort OR Prednidib OR Prednilonga OR Prednilonga OR Predniment OR Prednisone OR Prednisonum OR Prednitone OR Promifen OR Servisone OR Servisone OR 'Sk-Prednisone' OR Sterapred):ab,ti,kw
45	Samarium:ab,ti,kw
46	(Sipuleucelt OR 'APC8015 Vaccine' OR 'APC8015' OR 'PA2024 Loaded Dendritic Cell Vaccine' OR Provenge OR 'Sipuleucel-T' OR 'apc 8015'):ab,ti,kw
47	Strontium:ab,ti,kw
48	('Tak-700' OR 'Tak 700' OR 'Tak700'):ab,ti,kw
49	(Triptorelin OR '6-D-Tryptophan-LH-RH' OR '6-D-Tryptophanluteinizing Hormone-releasing Factor' OR ' AY-25650' OR 'CL-118,532' OR 'Decapeptyl' OR Detryptoreline OR 'd trp 6 lhrh' OR 'arvekap' OR 'ay 25650' OR 'ay25650' OR 'd trp 6 lhrh' OR 'd trp 6 luteinizing hormone releasing hormone' OR 'gonadorelin 6 dextro tryptophan' OR 'gonadotropin releasing hormone 6 dextro tryptophan' OR 'lhrh d trp 6' OR 'lhrh 6 dextro tryptophan' OR 'luteinizing hormone releasing hormone 6 dextro tryptophan' OR trelstar OR 'trelstar la' OR tryptorelin):ab,ti,kw
50	('le 29060' OR 'le29060' OR 'leukoblastin' OR rozevin OR 'vin blastine' OR vinblastin* OR vincaleucoblastin* OR vincaleukoblastin* OR vincoblastin* OR vincoleucoblastin* OR vincoleukoblastin* OR vinleucoblastine OR vlb):ab,ti,kw
51	(Navelbine OR vinorelbine OR '3,4-Didehydro-4-deoxy-C-norvincaleukoblastine' OR '5-Nor-Anhydrovinblastine' OR Dihydroxydeoxynorvinkaleukoblastine OR 'nor-5-Anhydrovinblastine'):ab,ti,kw
52	(zd4054 or 'zd 4054' or zibotentan or 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide'):ab,ti,kw
53	('zoledronic acid' OR zoledronate OR zometa OR reclast OR 'zol 446' OR 'cgp 42446'):ab,ti,kw
54	(AS1404 OR 'AS 1404' OR DMXAA OR 'as 1404' OR as1404 OR 'asa 404' OR asa404 OR 'nsc 640488' OR nsc640488):ab,ti,kw
55	(IMC-A12 OR Cixutumumab OR 'Anti-IGF-1R Recombinant Monoclonal Antibody IMC-A12'):ab,ti,kw
56	(patupilone OR 'epo 906' OR epo906 OR 'epothilon b'):ab,ti,kw
57	(Sunitinib OR 'pha 2909040ad' OR pha2909040ad OR 'su 010398' OR 'su 011248' OR 'su 10398' OR 'su 11248' OR su010398 OR su011248 OR su10398 OR su11248 OR sutent):ab,ti
58	('cab' OR 'complete androgen blockade'):ab,ti,kw
59	MeSH descriptor Adrenal Cortex Hormones explode all trees
60	MeSH descriptor Androgen Antagonists explode all trees
61	MeSH descriptor Gonadotropin-Releasing Hormone explode all trees
62	cancer immunotherapy
63	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62)
64	(#8 AND #63), Limited to 2012 to 2013, Economic and HTA filter

Table 121: Cochrane database search strategy (searched on 02.09.13)

#	Search string
1	MeSH descriptor Prostatic Neoplasms explode all trees
2	prostate tumor
3	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)
4	crpc
5	castrat* NEAR/3 resistant
6	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*
7	(#5 AND #6)
8	(#1 OR #2 OR #3 OR #4 OR #7)
9	('5-Fluorouracil' OR '5-Fluracil' OR '5-FU' OR AccuSite OR 'Actino-Hermal' OR Adrucil OR Arumel OR Cytosafe OR Efudex OR Efurix OR Fiverocil OR 'Fluoro Uracil' OR Fluoroplex OR Fluorouracil OR Fluouracil OR Flurablastin OR Fluracedyl OR Fluracil OR Fluril OR Fluroblastin OR Flurox OR Ribofluor OR 'Ro 2-9757' OR Timazin):ab,ti,kw
10	(Abarelix OR Plenaxis OR 'PPI 149' OR 'R 3827' OR PPI149 OR R3827):ab,ti,kw

#	Search string
11	(Abiraterone OR 'cb 7598' OR cb7598):ab,ti,kw
12	(Aflibercept OR 'AVE0005' OR 'Vascular Endothelial Growth Factor Trap' OR 'VEGF Trap R1R2' OR 'VEGF Trap' OR 'vasculotropin trap'):ab,ti,kw
13	(Aminoblastin OR Aminoglutethimide OR 'BA-16038' OR 'Ba-16038' OR Cytadren OR Elipten OR Mamomit OR Orimenten* OR Orimeten OR Rodazol):ab,ti,kw
14	('abt 627' or atrasentan or xinlay or abt627 or 'a 147627' or a147627 or a1277* or a NEXT/1 1277*):ab,ti,kw
15	(Bevacizumab OR avastin OR 'nsc 704865' OR nsc704865 OR 'anti-vegf' OR 'Anti-VEGF Humanized Monoclonal Antibody' OR 'Anti-VEGF rhuMAb' OR 'Recombinant Humanized Anti-VEGF Monoclonal Antibody' Or 'rhuMab-VEGF'):ab,ti,kw
16	(Bicalutamide OR Casodex OR Cosudex OR 'ICI 176334' OR ICI176334 OR raffolutil):ab,ti,kw
17	(Cabazitaxel OR RPR-116258A OR 'Taxoid XRP6258' OR XRP6258):ab,ti,kw
18	(Blastocarb OR Carboplatin OR Carboplat* OR Carbosin OR Carbosol OR Carbotec OR CBDCA OR Displata OR Ercar OR 'JM-8' OR Nealorin OR Novoplatinum OR Paraplat* OR Platinwas OR Ribocarbo):ab,ti,kw
19	('nsc 81340' OR 'nsc 81430' OR nsc81340 OR nsc81430 OR 'sh 714' OR sh714 OR sinovir OR virilit OR cyproterone):ab,ti,kw
20	(dasatinib OR 'bms 354825' OR bms354825 OR sprycel):ab,ti,kw
21	(Degarelix OR FE200486 OR 'FE 200486'):ab,ti,kw
22	(dexamethasone OR 'aeroseb dex' OR aflucoson* OR anaflog* OR arcodex* OR azium OR calonat OR cebedex OR colofoam OR cortidron* OR cortisumman OR (dacort* NEAR/1 fue*) OR dalalone OR decilone OR decofluor OR dectancyl OR decacort* OR dekacort* OR delladec OR deltafluoren OR dergramin OR deronil OR desadrene OR desalark OR desameto* OR dexa* OR dexinoral OR dexionil OR dexone OR dextelan OR dezone OR d?xamethasone OR esacortene OR 'ex s1' OR exadion* OR firmalone OR (fluor* NEAR/1 predniso*) OR fluormethylpredniso* OR fluormone OR fluorocort OR fluorodelta OR fortecortin OR gammacorten* OR grosodexon* OR dexa* OR hexadecad* OR hexadiol OR hexadrol OR isnacort OR isopto* OR 'lokalison f' OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson* OR metasolon* OR methazon* OR 'metisone lafi' OR millicorten* OR nisomethasona OR novocort OR opticort* OR oradex* OR orgadrone OR policort OR posurdex OR 'predni f tablinen' OR 'prednisolone f' OR prodex* OR sanamethasone OR spoloven OR triamcimetil OR visumethazone OR decadeltosona OR decadeltosone OR decadion* OR decadran OR decadron* OR decaesadril OR decamethasone OR decasone OR decaspray OR decasterolone):ab,ti,kw
23	(Acnestrol OR 'Alpha,alpha-diethylstilbenediol' OR Antigestil OR Apstil OR Boestrol OR Bufon OR 'Cyren A' OR DES OR Diastyl OR Diethylstilbenediol OR Diethylstilbestrolum OR diethylstilbestrol OR Diethylstilboestrol OR Distilbene OR Domestrol OR Estrobene OR Estromenin OR Estrosyn OR Fonatol OR Grafestrol OR Makarol OR Microest OR Milestrol OR 'Neo-Oestronol I' OR Oestrogeni* OR Oestromenin OR Oestromensyl OR Oestromon OR Palestrol OR Serral OR Sexocretin OR Sibol OR Stilbestro* OR Stilbetin OR Stilboefral OR Stilboestrol OR Stilkap OR Synestrin OR Synthoestrin OR Vagestrol OR Vagestrol OR Hexanestrol OR hexestrofen OR hexital OR hexron OR hexypheen OR 'hi bestrol' OR 'hormoestrol' OR menostilbene OR 'meso hexestrol' OR mesohexestrol OR micrest OR 'neo estranol' OR 'nsc 3070' OR 'nsc 35752' OR 'nsc 9894' OR oekolp OR oestrostilben OR oestrosyntal OR orestrol OR ovendosyn OR pabestrol OR pabestrosalve OR palestrol OR proestrin OR serral):ab,ti,kw
24	(Docetaxel OR Taxotere):ab,ti,kw
25	(doxorubicin OR 'Hydroxyl Daunorubicin' OR adriablastin* OR adriacin OR adriam?cina OR adriamycin OR adriblastin* OR caelyx OR dexorubicin OR 'dox sl' OR doxil OR doxorubicin* OR 'fi 106' OR lipodox OR 'liposomal doxorubicin' OR myocet OR 'nsc 123127' OR 'pegylated liposomal doxorubicin' OR rastocin OR resmycin OR 'rp 25253' OR rubex OR sarcodoxome OR 'tlc d 99'):ab,ti,kw
26	(Dutasteride OR 'GG 745' OR 'GG745' OR Avodart OR Avolve OR advodart OR duagen OR 'gi 198745' or gi198745*):ab,ti,kw
27	(e7389 or 'e 7389' or eribulin or 'halichondrin b analog'):ab,ti,kw
28	(Estramustine OR 'Leo 275' OR 'RO 21 8837' OR 'leo 462' OR 'nsc 89199' OR 'ro 21 8837' OR 'ro 22 2296 000' OR Leo275 OR RO218837 OR Leo462 OR nsc89199 OR ro218837 OR ro222296000):ab,ti,kw
29	(EPEG OR Etoposide OR Lastet OR Vepesid OR 'VP 16-213' OR etomedac OR etopol OR lastet OR 'nk 171' OR 'nsc 141540' OR toposar OR vepesid*):ab,ti,kw
30	('Chibro-Proscar' OR Finasteride OR Finastid OR 'MK 906' OR 'Pro-Cure' OR Propecia OR Propeshia OR Proscar OR Prostide OR Urprosan OR 'ym 152'):ab,ti,kw
31	(Flutamide OR Apimid OR Chimax OR Drogenil OR Euflex OR Eulexine OR Eulexin OR Flucinome OR Flucinom OR Flugerel OR Fluken OR Flulem OR 'Fluta-Gry' OR Flutabene OR Flutacan OR Flutamex OR Flutamin OR Flutan OR Flutaplex OR FLUT OR Fugerel OR Grisetin OR Niftolid OR Oncosal OR Profamid OR Prostacur OR Prostadirex OR Prostica OR Prostogenat OR 'SCH 13521' OR Sch13521 OR Tafenil OR Tecnoflut OR Testotard OR drogenil OR euflex OR eulexin OR flumid OR niftolid OR niphtholid OR sebatrol):ab,ti,kw
32	(Goserelin OR 'ICI-118630' OR 'ici 118 630' OR 'ici 118630' OR ici118630 OR zoladex):ab,ti,kw
33	('Aeroseb-HC' OR 'Barseb HC' OR Cetacort OR 'Cort-Dome' OR Cortef OR Cortenema OR Cortifan OR Cortisol OR Cortispray OR Cortril OR Dermacort OR Domolene OR Eldecort OR Hautosone OR 'Heb-Cort' OR Hydrocortisone OR Hydrocortone OR Hytone OR 'Komed-HC' OR Nutracort OR Proctocort OR Rectoid OR Therapeutic Hydrocortisone OR alphaderm OR barseb OR cetacort OR cobadex OR 'compound f' OR cortef OR cortenema OR cortibel OR cortifan OR cortifoam OR cortiment OR cortiphate OR cortisol* OR cortoderm OR cortril OR dermolate OR dioderm OR duomedihaler OR 'ef cortelan' OR efcortelan OR egocort OR eksalb OR eldecort OR ficortril OR hebcort OR hycort OR hydracort OR hydrasson OR 'hydro ricortex' OR hydrocort OR hydrocorticosteroid OR hydrocortisate OR hydrocortis* OR hydrocortone OR hydroderm OR hysone OR hytone OR incortin OR medihaler OR mildison OR munitren 'neo cortef' OR neocortef OR novohydrocort OR 'nsc 10483' OR 'nsc 741' OR nutracort OR otosone OR penecort OR prepcort OR proctocort OR proctosone OR rectocort OR schericur OR 'scherosone f' OR 'solu cortef' OR synacort OR vasocort):ab,ti,kw
34	('Anti-Cytotoxic T-Lymphocyte-Associated Antigen-4 Monoclonal Antibody' OR Ipilimumab OR 'MDX-010' OR 'MDX-CTLA4' OR 'bms 734016'):ab,ti,kw
35	(JM216 OR 'JM 216'):ab,ti,kw

#	Search string
36	(Ketoconazole OR Fungarest OR Fungoral OR Ketoderm OR Ketoisdin OR Nizoral OR Orifungal OR Panfungol OR Xolegel OR Anisole OR cetonax OR 'dio 902' OR dio902 OR 'kw 1414' OR kw1414 OR micoral OR nisoral OR oxocanazole OR oxoconazole OR 'r 41 400' OR r41400 OR terzolin):ab,ti,kw
37	(leuprolide or leuprorelin or leuplin or leupro* OR lucrin OR lupride OR lupron OR procrin OR prostap OR tap144 or 'tap 144'):ab,ti,kw
38	(Mdv3100 OR 'mdv3100'):ab,ti,kw
39	(megestrol):ab,ti,kw
40	(Mitoxantrone OR Dihydroxyanthracenedione OR Mito?antrone OR novanthron OR novantron* OR 'now 85 34' OR 'now 8534' OR now8534 OR 'nsc 279836' OR 'nsc 301739' OR 'nsc 301739d' OR nsc279836 OR nsc301739 OR nsc301739d):ab,ti,kw
41	(Nilutamide OR Anandron OR Nilandron OR anadron OR nitulamide OR 'rn 23908' OR 'ru 23908' OR rn23908 OR ru23908):ab,ti,kw
42	('abi 007' OR 'abi007' OR abraxane OR anzatax OR 'bms 181339' OR coroxane OR genexol OR hunxol OR intaxel OR 'nsc 125973' OR paxceed OR paclitaxel OR paxene OR taxol OR yewtaxan OR Anzatax OR Asotax OR Bristaxol OR Praxel):ab,ti,kw
43	('pamidronic acid' OR pamidronate OR aredia OR aminomux OR 'gcp-23339a'):ab,ti,kw
44	(prednison* OR prednisolon* OR Adasone OR Cortancyl OR Dacortin OR Dacortin OR 'De Cortin' OR DeCortin OR 'De cortisyl ' OR Decortisyl OR Decorton OR Decorton OR 'Delta-Cortisone' OR ' Delta-Dome' OR 'Delta-Dome' OR Deltacortene OR Deltacortisone OR Deltacortisone OR Deltadehydrocortisone OR Deltasone OR Deltasone OR Deltison OR Deltison OR Deltra OR Econosone OR Lisacort OR 'Meprosona-F' OR Metacortandracin OR Metacortandracin OR Meticorten OR Meticorten OR Ofisolona OR Orasone OR Orasone OR Panafcort OR 'Panasol-S' OR Paracort OR Predeltin OR Predicorten OR Predicor OR 'Prednicen-M' OR Prednicort OR Prednidib OR Prednilonga OR Prednilonga OR Predniment OR Prednisone OR Prednisonum OR Prednitone OR Promifen OR Servisone OR Servisone OR 'Sk-Prednisone' OR Sterapred):ab,ti,kw
45	Samarium:ab,ti,kw
46	(Sipuleucelt OR 'APC8015 Vaccine' OR 'APC8015' OR 'PA2024 Loaded Dendritic Cell Vaccine' OR Provenge OR 'Sipuleucel-T' OR 'apc 8015'):ab,ti,kw
47	Strontium:ab,ti,kw
48	('Tak-700' OR 'Tak 700' OR 'Tak700'):ab,ti,kw
49	(Triptorelin OR '6-D-Tryptophan-LH-RH' OR '6-D-Tryptophanluteinizing Hormone-releasing Factor' OR ' AY-25650' OR 'CL-118,532' OR 'Decapeptyl' OR Detryptoreline OR 'd trp 6 lhrh' OR 'arvekap' OR 'ay 25650' OR 'ay25650' OR 'd trp 6 lhrh' OR 'd trp 6 luteinizing hormone releasing hormone' OR 'gonadorelin 6 dextro tryptophan' OR 'gonadotropin releasing hormone 6 dextro tryptophan' OR 'lhrh d trp 6' OR 'lhrh 6 dextro tryptophan' OR 'luteinizing hormone releasing hormone 6 dextro tryptophan' OR trelstar OR 'trelstar la' OR tryptorelin):ab,ti,kw
50	('le 29060' OR 'le29060' OR 'leukoblastin' OR rozevin OR 'vin blastine' OR vinblastin* OR vincaleucoblastin* OR vincaleukoblastin* OR vincoblastin* OR vincoleucoblastin* OR vincoleukoblastin* OR vinleucoblastine OR vlb):ab,ti,kw
51	(Navelbine OR vinorelbine OR '3,4-Didehydro-4-deoxy-C-norvincaleukoblastine' OR '5-Nor-Anhydrovinblastine' OR Dihydroxydeoxynorvinkaleukoblastine OR 'nor-5-Anhydrovinblastine'):ab,ti,kw
52	(zd4054 or 'zd 4054' or zibotentan or 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide'):ab,ti,kw
53	('zoledronic acid' OR zoledronate OR zometa OR reclast OR 'zol 446' OR 'cgp 42446'):ab,ti,kw
54	(AS1404 OR 'AS 1404' OR DMXAA OR 'as 1404' OR as1404 OR 'asa 404' OR asa404 OR 'nsc 640488' OR nsc640488):ab,ti,kw
55	(IMC-A12 OR Cixutumumab OR 'Anti-IGF-1R Recombinant Monoclonal Antibody IMC-A12'):ab,ti,kw
56	(patupilone OR 'epo 906' OR epo906 OR 'epothilon b'):ab,ti,kw
57	(Sunitinib OR 'pha 2909040ad' OR pha2909040ad OR 'su 010398' OR 'su 011248' OR 'su 10398' OR 'su 11248' OR su010398 OR su011248 OR su10398 OR su11248 OR sutent):ab,ti
58	('cab' OR 'complete androgen blockade'):ab,ti,kw
59	MeSH descriptor Adrenal Cortex Hormones explode all trees
60	MeSH descriptor Androgen Antagonists explode all trees
61	MeSH descriptor Gonadotropin-Releasing Hormone explode all trees
62	cancer immunotherapy
63	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62)
64	(#8 AND #63), Limited to 2013 to 2013, Economic and HTA filter

Table 122: MEDLINE In-process search strategy (searched on 20.11.12)

#	Search string
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotronei OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyte
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'

#	Search string
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100
21	Search aflibercept OR 'vegf trap'
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010'
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search triptorelin or arvekap
37	Search TAK-700
38	Search samarium
39	Search nilutamide OR nilandron
40	Search megestrol
41	Search leuprorelin OR procrin
42	Search ketoconazole or fungarest
43	Search goserelin OR zoladex
44	Search flutamide OR eulexin
45	Search Finasteride OR propecia
46	Search e7389 OR eribulin mesylate
47	Search diethylstilbestrol OR ekol
48	Search diethystilbesterol OR oekolp
49	Search dutasteride OR avodart
50	Search degarelix
51	Search cyproterone acetate
52	Search CAB
53	Search bicalutamide OR casodex
54	Search Aminoglutethimide OR Elipten
55	Search abarelix or plenaxis

#	Search string
56	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
57	Search #3 AND #56
58	Search #57 AND in process[sb]

Table 123: MEDLINE In-process search strategy (searched on 30.05.13)

#	Search string
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotronei OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyte
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100
21	Search aflibercept OR 'vegf trap'
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010'
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'

#	Search string
36	Search triptorelin or arvekap
37	Search TAK-700
38	Search samarium
39	Search nilutamide OR nilandron
40	Search megestrol
41	Search leuprorelin OR procrin
42	Search ketoconazole or fungarest
43	Search goserelin OR zoladex
44	Search flutamide OR eulexin
45	Search Finasteride OR propecia
46	Search e7389 OR eribulin mesylate
47	Search diethylstilbestrol OR ekol
48	Search diethystilbesterol OR oekolp
49	Search dutasteride OR avodart
50	Search degarelix
51	Search cyproterone acetate
52	Search CAB
53	Search bicalutamide OR casodex
54	Search Aminoglutethimide OR Elipten
55	Search abarelix or plenaxis
56	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
57	Search #3 AND #56
58	Search #57 AND in process[sb]

Table 124: MEDLINE In-process search strategy (searched on 02.09.13)

#	Search string
1	Search prostat*
2	Search cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR adenocarcinoma* OR intraepithelial
3	Search #1 AND #2
4	Search docetaxel OR taxotere OR 'rp 56976' OR rp56976
5	Search mito?antrone OR novant* OR mitroxone OR neotalemti OR onkotronei OR pralifan OR dhad OR dhaq
6	Search estramustine OR emcyt OR estracyte
7	Search fluorouracil OR 'fluoro uracil' OR fluouracil OR fu OR adrucil OR efudex OR fluoroplex OR accusite OR 'actino hermal' OR arumel OR cytosafe OR efurix OR fiverocil OR flur?blastin OR fluracedyl OR fluracil OR fluril OR flurox OR ribofluor OR timazin OR 'ro 2 9757'
8	Search paraplat* OR blastocarb OR carboplat* OR carbosin OR carbosol OR carbotec OR displata OR ercar OR nealorin OR novoplatinum OR platinwas OR ribocarbo OR cbdca OR 'jm 8'
9	Search cyclophospham* OR ciclofosfamida OR ciclofosfamide OR claphene OR cp OR cpm OR cyclophosphan* OR cytophosphane OR mitoxan OR syklofosfamid OR zytoxan OR clafen OR cytoxan OR neosar OR carloxan OR cicloxal OR cycloblastin* OR 'cyclo cell' OR cyclostin OR cyclostine:ab,ti OR cytophosphan OR endoxan* OR enduxan OR fosfaseron OR genoxal OR ledoxina OR procytox OR sendoxan OR ctx OR 'asta b 518' OR 'b 518' OR 'wr 138719'
10	Search doxorubicin OR adr OR adriblastin* OR adrimedac OR 'doxo cell' OR doxolem OR doxorubin OR farmiblastina OR rubex OR adm OR adria* OR dox OR 'fi 106' OR doxil OR 'dox sl' OR evacet OR lipodox OR caelyx OR doxilen OR 'tlc d 99'
11	Search etoposide OR toposar OR vepesid OR lastet OR epeg OR 'vp 16' OR 'vp 16 213'
12	Search paclitaxel OR taxol OR anzatax OR asotax OR bristaxol OR praxel OR 'taxol konzentrat'
13	Search vinorelbine OR navelbine OR 'anx 530' OR biovelbin OR eunades OR nvb OR vnb OR 'kw 2307'
14	Search vinblastine OR vincaleucoblastine OR velban OR velsar OR vlb
15	Search hydrocortisone OR cortifan OR orcortisol OR domolene OR 'barseb hc' OR 'komed hc' OR 'aeroseb hc' OR cetacort OR 'cort dome' OR cortef OR cortenema OR cortispray OR cortril OR dermacort OR eldecort OR hydrocortone OR hytone OR nutracort OR protocort OR rectoid
16	Search prednisone OR deltacortisone OR 'delta cortisone' OR deltadehydrocortisone OR metacortandracin OR prednisonum OR deltasone OR 'delta dome' OR 'liquid pred' OR lisacort OR meticorten OR orasone OR prednicen OR sterapred OR adasone OR cortancyl OR dacortin OR decortin OR decortisyl OR decorton OR deltacortene OR deltison OR deltra OR econosone OR meprosona OR ofisolona OR panafcort OR panasol OR paracort OR predeltin OR predicor* OR prednidib OR prednilonga OR predniment OR prednitone OR promifen OR servisone
17	Search prednisolone OR metacortandralone OR cortalone OR 'delta cortef' OR hydeltra OR hydeltrasol OR 'meti derm' OR 'prelone' OR adnisolone OR aprednislon OR capsoid OR cortisolone OR dacortin OR decaprednil OR deltacortril OR deltasolone OR deltidrosol OR dhasolone OR dontisolon OR estilsona OR fisopred OR frisolona OR gupisone OR hostacortin OR klismacort OR kuhlprednon OR lenisolone OR 'lepi cortinolo' OR linola OR longiprednil OR meticortelone OR opredsone OR panafcortelone OR precortisyl OR 'pred clysma' OR predeltilone OR 'predni coelin' OR prednicortelone OR 'predni helvacort' OR prenilone

#	Search string
18	Search de?amethason* OR dxm OR hexadecadrol OR 'aeroseb dex' OR 'alba dex' OR decaderm OR decadrol OR decadron OR decasone OR decaspray OR 'dex 4' OR dexace OR dexameth OR deenar OR deronil OR dezone OR gammacorten OR hexadrol OR maxidex OR aacidexam OR adexone OR aknichthol OR alin OR ambene OR amplidermis OR 'anemul mono' OR antimicotico OR aquapred OR auricularum OR auxiloson OR azona OR baycuten OR corson OR cortidexason OR cortisumman OR de?acort OR decalix OR dectancyl OR deltafluorene OR desameton OR dexacortal OR dexacortin OR dexafarma OR dexafluorene OR dexalocal OR dexamecortin OR dexamonozon OR dexapos OR dexinoral OR dexone OR dinormon OR fortecortin OR 'lokalison f' OR loverine OR millicorten OR mymethasone OR ocasa OR orgadrone OR 'predni f' OR spersadex OR visumetazone
19	Search abirateron* OR 'cb 7598' OR cb7598 OR zytiga
20	Search 'mdv 3100' OR mdv3100
21	Search aflibercept OR 'vegf trap'
22	Search as1404 OR 'dimethyloxoxanthene acetic acid' OR dmxaa OR asa404
23	Search atrasentan OR xinlay
24	Search bevacizumab OR avastin
25	Search cabazitaxel OR 'taxoid xrp6258' OR 'rpr 116258a' OR xrp6258
26	Search dasatinib OR sprycel OR 'bms 354825' OR bms354825
27	Search cixutumumab OR 'imc a12'
28	Search satraplatin OR orplatna OR 'bms 182751' OR 'bmy 45594' OR jm216
29	Search 'zd 4054' OR zd4054
30	Search provenge OR 'sipuleucel t'
31	Search ipilimumab OR 'ctla 4' OR ctla4 OR 'mdx 010'
32	Search epothilone OR patupilone OR epo906
33	Search sunitinib OR sutent OR su011248 OR su11248
34	Search strontium OR metastron OR sr89
35	Search zoledron* OR zometa OR 'cgp 42446' OR cgp42446a OR 'zol 446'
36	Search triptorelin or arvekap
37	Search TAK-700
38	Search samarium
39	Search nilutamide OR nilandron
40	Search megestrol
41	Search leuprorelin OR procrin
42	Search ketoconazole or fungarest
43	Search goserelin OR zoladex
44	Search flutamide OR eulexin
45	Search Finasteride OR propecia
46	Search e7389 OR eribulin mesylate
47	Search diethylstilbestrol OR ekol
48	Search diethystilbesterol OR oekolp
49	Search dutasteride OR avodart
50	Search degarelix
51	Search cyproterone acetate
52	Search CAB
53	Search bicalutamide OR casodex
54	Search Aminoglutethimide OR Elipten
55	Search abarelix or plenaxis
56	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
57	Search #3 AND #56
58	Search #57 AND in process[sb]

Table 125: Econlit search strategy (searched on 20.11.12)

#	Search string
1	Prostate
2	Prostate cancer
3	CRPC
4	HRPC
5	Castrate
6	Prostate tumor
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (year 2000 to 2011)

Table 126: Econlit search strategy (searched on 30.05.13)

#	Search string
1	Prostate
2	Prostate cancer
3	CRPC
4	HRPC
5	Castrate

6	Prostate tumor
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (year 2011 to 2013)

Table 127: Econlit search strategy (searched on 02.09.13)

#	Search string
1	Prostate
2	Prostate cancer
3	CRPC
4	HRPC
5	Castrate
6	Prostate tumor
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (year 2013 to 2013)

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Health technology assessment agency websites were searched, on the 22.12.09, 14.06.11, 28.03.12, 22.11.12 and 18.07.13, to retrieve data on the relevant pharmacoeconomic data and analyses submitted to these agencies. The HTA agencies that were searched for the submissions in metastatic prostate cancer are described in Table 128.

Table 128: Countries and agencies searched for the HTA review

Country	Agencies	Website
Australia	Pharmaceutical benefits advisory committee	http://www.healthyactive.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-listing-committee3.htm
	Medical Services Advisory Committee	http://www.msac.gov.au/
Canada	Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca/index.php/en/home
United Kingdom	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
	Scottish Medicines Consortium	http://www.scottishmedicines.org.uk/smc/CCC_FirstPage.jsp
	National institute for Health Research Health Technology Assessment programme	http://www.hta.ac.uk/
United States	Economic Cycle Research Institute	https://www.ecri.org/Pages/default.aspx
	Agency for Healthcare Research and Quality	http://www.ahrq.gov/
Global	International Network of Agencies for Health Technology Assessment	http://www.inahta.org/

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

N/A.

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **NHS Economic Evaluation Database (NHS EED)**
- **EconLIT.**

The specific databases searched and the service providers used for the systematic search to identify relevant data on the measurement and valuation of health effects are shown in Table 129.

Table 129: Literature databases searched with the service provider used

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 TA101 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 above. The translated searches were validated by confirming that they returned the seven studies identified and included in the QoL review of the TA101 assessment.

Please note that the EconLit® database was searched via the AEAweb.org platform in a previous review of the HRQL of patients with advanced metastatic prostate cancer, with no studies meeting the inclusion criteria identified. This was also the procedure used to perform the systematic search of HRQL data in the earlier NICE STA submission for abiraterone acetate for the treatment of mCRPC following previous cytotoxic therapy [61].

10.12.2 The date on which the search was conducted.

02.09.13.

10.12.3 The date span of the search.

01.01.05 to 02.09.13.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 130: Embase.com search strategy

#	Search string
#1	'prostate tumor'/exp OR ((prostate OR prostatic) NEAR/2 (neoplasm OR neoplasm$ OR cancer OR cancer$ OR carcinoma OR carcinoma$ OR adenocarcinoma OR adenocarcinoma$ OR tumour OR tumour$ OR tumor OR tumor$)):ab,ti
#2	(utilit* NEAR/1 approach*):ab,ti OR (health NEAR/1 gain):ab,ti OR hui:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 'hui 3':ab,ti OR health:ab,ti AND (measurement* NEAR/1 (scale* OR questionnaire*)):ab,ti OR 'standard gamble':ab,ti OR 'standard gambles':ab,ti OR (categor* NEXT/1 scal*):ab,ti OR (linear NEXT/1 analog*):ab,ti OR (visual NEXT/1 scal*):ab,ti OR (magnitude NEXT/1 estimat*):ab,ti OR (time NEXT/1 (tradeoff OR tradeoffs OR trade$off OR trade$offs)):ab,ti OR (rosser* NEXT/1 (classif* OR matrix OR distress*)):ab,ti OR hrqol:ab,ti OR 'index of wellbeing':ab,ti OR 'quality of wellbeing':ab,ti OR qwb:ab,ti OR (multiattribute*:ab,ti OR 'multi-attribute':ab,ti OR 'multi-attributed':ab,ti OR 'multi-attributes':ab,ti OR 'multi attribute':ab,ti OR 'multi attributed':ab,ti OR 'multi attributes':ab,ti AND (health NEXT/1 ind*):ab,ti) OR 'health utility index':ab,ti OR 'health utilities index':ab,ti OR 'health utility indices':ab,ti OR 'health utilities indices':ab,ti OR ((multiattriattribute* OR 'multi-attribute' OR 'multi-attributed' OR 'multi-attributes' OR 'multi attribute' OR 'multi attributed' OR 'multi attributes') NEXT/1 (theor* OR analys*)):ab,ti OR (('health utility' OR 'health utilities') NEXT/1 scale*):ab,ti OR ('classification of illness' NEXT/1 state*):ab,ti OR (15 NEXT/1 dimension):ab,ti OR 'health state utility':ab,ti OR 'health states utility':ab,ti OR 'health state utilities':ab,ti OR 'health states utilities':ab,ti OR (well NEXT/1 year*):ab,ti OR ((multiattriattribute* OR 'multi-attribute' OR 'multi-attributed' OR 'multi-attributes' OR 'multi attribute' OR 'multi attributed' OR 'multi attributes') NEXT/1 utilit*):ab,ti OR 'health utility scale':ab,ti OR 'health utility scales':ab,ti OR 'health utilities scale':ab,ti OR 'health utilities scales':ab,ti OR 'euro qol':ab,ti OR 'euro qual':ab,ti OR 'eq-5d':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR euroqol:ab,ti OR euroqoi:ab,ti OR euroqual:ab,ti OR qualy:ab,ti OR qaly:ab,ti OR qualys:ab,ti OR qalys:ab,ti OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR 'willingness to pay':ab,ti OR hye:ab,ti OR hyes:ab,ti OR (health*:ab,ti AND (year* NEXT/1 equivalent*):ab,ti) OR ((person OR time) NEAR/1 (tradeoff OR tradeoffs OR trade$off OR trade$offs)):ab,ti OR (theory NEXT/1 utilit*):ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR 'sf 6d':ab,ti OR 'short form 6d':ab,ti
#3	#1 AND #2 AND [2005-2012]/py

Table 131: Cochrane® (NHSEED) search strategy

#	Search string
#1	MeSH descriptor Prostatic Neoplasms explode all trees
#2	(prostate OR prostatic) NEAR/2 (neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR tumour* OR tumor*)
#3	(utilit* NEAR/1 approach*) OR (health NEAR/1 gain) OR hui OR hui2 OR hui3 OR (hui NEAR/1 3) OR (health NEXT measurement* NEXT (scale* OR questionnaire*)) OR (standard NEAR/1 gamble*) OR (categor* NEAR/1 scal*) OR (linear NEAR/1 scal*) OR (linear NEAR/1 analog*) OR (visual NEAR/1 scal*) OR (magnitude NEAR/1 estimat*) OR (time NEAR/1 (tradeoff OR tradeoffs OR "trade off" OR "trade offs")) OR (rosser* NEAR/1 (classif* OR matrix OR distress*)) OR hrqol OR (index NEAR/2 wellbeing) OR (quality NEAR/2 wellbeing) OR qwb OR (multiattribute* NEXT health NEXT ind*) OR (multi NEXT attribute NEXT health NEXT ind*) OR (health NEXT utilit* NEXT index) OR (health NEXT utilit* NEXT indices)
#4	(multiattribute* NEAR/1 theor*) OR (multi NEXT attribute* NEXT theor*) OR (multiattribute* NEAR/1 analys*) OR (multi NEXT attribute* NEXT analys*) OR (health NEXT utilit* NEXT scale*) OR (classification NEXT of NEXT illness NEXT state*) OR (15 NEAR/1 dimension) OR (health NEXT state* NEXT utilit*) OR (well NEAR/1 year*) OR (multattribute* NEAR/1 utilit*) OR (multi NEXT attribute* NEXT utilit*) OR (health NEXT utilit* NEXT scale*) OR "euro qol" OR "euro qual" OR "eq-5d" OR eq5d OR "eq 5d" OR euroqol OR euroqoi OR euroqual OR qualy OR qaly OR qualys OR qalys OR "quality adjusted life year" OR "quality adjusted life years" OR "willingness to pay"
#5	hye OR hyes OR (health* NEXT year* equivalent*) OR (person NEXT trade NEXT off*) OR (person NEAR/1 tradeoff*) OR (time NEAR/1 tradeoff*) OR (time NEXT trade NEXT off*) OR (theory NEAR/1 utilit*) OR sf36 OR (sf NEAR/1 36) OR (short NEXT form NEXT 36) OR (shortform NEAR/1 36) OR (sf NEAR/1 thirtysix) OR (sf NEXT thirty NEXT six) OR (shortform NEAR/1 thirtysix) OR (shortform NEXT thirty NEXT six) OR (short NEXT form NEXT thirtysix) OR (short NEXT form NEXT thirty NEXT six) OR (sf NEAR/1 6d) OR (short NEXT form NEXT 6d)
#6	((#1 OR #2) AND (#3 OR #4 OR #5))
#7	(#6) [NHS EED only]
#8	#1 AND #2 AND [2005-2012]/py [NHS EED only]

Table 132: PubMed® search strategy

#	Search string
#1	((prostate[TIAB] OR prostatic[TIAB]) AND (neoplasm*[TIAB] OR cancer*[TIAB] OR carcinoma*[TIAB] OR adenocarcinoma*[TIAB] OR tumour*[TIAB] OR tumor*[TIAB]))

#2	(utilit*[TIAB] AND approach*[TIAB]) OR “health gain”[TIAB] OR hui[TIAB] OR hui2[TIAB] OR hui 2[TIAB] OR hui3[TIAB] OR hui 3[TIAB] OR “health measurement scale”[TIAB] OR “health measurement scales”[TIAB] OR “health measurements scale”[TIAB] OR “health measurements scales”[TIAB] OR “health measurement questionnaire”[TIAB] OR “health measurement questionnaires”[TIAB] OR “health measurements questionnaire”[TIAB] OR “health measurements questionnaires”[TIAB] OR “standard gamble”[TIAB] OR “standard gambles”[TIAB] OR (category*[TIAB] AND scal*[TIAB]) OR (linear[TIAB] AND analog*[TIAB]) OR (visual[TIAB] AND scal*[TIAB]) OR (magnitude[TIAB] AND estimate*[TIAB]) OR “time trade off”[TIAB] OR “time trade offs”[TIAB] OR “time traderoff”[TIAB] OR “time tradeoffs”[TIAB] OR (rosser*[TIAB] AND classif*[TIAB]) OR (rosser*[TIAB] AND matrix[TIAB]) OR (rosser*[TIAB] AND distress*[TIAB]) OR hrqol[TIAB] OR “index of wellbeing”[TIAB] OR “quality of wellbeing”[TIAB] OR qwb[TIAB] OR (“multiattribute*[TIAB] AND health[TIAB] AND ind*[TIAB]) OR (“multi attribute*[TIAB] AND health[TIAB] AND ind*[TIAB]) OR “health utility index”[TIAB] OR “health utilities index”[TIAB] OR “health utility indices”[TIAB] OR “health utilities indices”[TIAB] OR (“multiattribute*[TIAB] AND theor*[TIAB]) OR (“multi attribute*[TIAB] AND analys*[TIAB]) OR “health utility scale”[TIAB] OR “health utility scales”[TIAB] OR “health utilities scale”[TIAB] OR health utilities scales”[TIAB] OR “classification of illness state”[TIAB] OR “classification of illness states”[TIAB] OR “15 dimension”[TIAB] OR “health state utility”[TIAB] OR “health states utility”[TIAB] OR “health state utilities”[TIAB] OR “health states utilities”[TIAB] OR “well year”[TIAB] OR “well years”[TIAB] OR (multiattribute*[TIAB] AND utilit*[TIAB]) OR (“multi attribute*”[TIAB] AND utilit*[TIAB]) OR “health utility scale”[TIAB] OR “health utility scales”[TIAB] OR “health utilities scale”[TIAB] OR “health utilities scales”[TIAB] OR “euro qol”[TIAB] OR “euro qual”[TIAB] OR “eq-5d”[TIAB] OR eq5d[TIAB] OR “eq 5d”[TIAB] OR euroqol[TIAB] OR euroqoi[TIAB] OR euroqual[TIAB] OR qualy[TIAB] OR qaly[TIAB] OR qualys[TIAB] OR qalys[TIAB] OR “quality adjusted life year”[TIAB] OR “quality adjusted life years”[TIAB] OR “willingness to pay”[TIAB] OR hye[TIAB] OR hyes[TIAB] OR “health year equivalent”[TIAB] OR “health year equivalents”[TIAB] OR “health years equivalent”[TIAB] OR “health years equivalents”[TIAB] OR “person trade off”[TIAB] OR “person trade offs”[TIAB] OR “person tradeoff”[TIAB] OR person tradeoffs”[TIAB] OR “theory utility*”[TIAB] OR “theory utilities*”[TIAB] OR Sf36[TIAB] OR “sf 36”[TIAB] OR “short form 36”[TIAB] OR “shortform 36”[TIAB] OR “sf thirtysix”[TIAB] OR “sf thirty six”[TIAB] OR “shortform thirtysix”[TIAB] OR “shortform thirty six”[TIAB] OR “short form thirtysix”[TIAB] OR “short form thirty six”[TIAB] OR “sf 6d”[TIAB] OR “short form 6d”[TIAB]
#3	#1 AND #2
#4	#3 AND in process[sb]

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were conducted.

10.12.6 The inclusion and exclusion criteria.

Studies reporting the utility or HRQL (assessed using specific instruments) on patients diagnosed with advanced or metastatic prostate cancer were included. The inclusion criteria used in this review are broader than those used in the HRQL review of the TA101 assessment, but the same as those used in the systematic search of HRQL data in the earlier NICE STA submission for abiraterone acetate for the treatment of mCRPC following previous cytotoxic therapy [61]. The eligibility criteria are described in Table 133.

Table 133: Exclusion criteria

Exclusion code	Question
Review/editorial	Commentaries, editorials, and reviews were not of interest. Only primary studies were included in this review
Animal/in vitro	Only studies in humans were of interest
Children (<18 years of age)	An adult population was of interest due to the disease area Studies in a mixed population of children and adults were only included if subgroup analyses were presented for adults
Disease	Only studies of patients diagnosed with prostate cancer were included

Stage of disease	Patients with advanced or metastatic prostate cancer were of interest Studies evaluating patients with early stage prostate cancer were excluded Studies of mixed population based on the stage of disease were only included if results for patients with advanced/metastatic prostate cancer were presented *NOTE: studies reporting HRQL/PRO data in populations diagnosed with 'locally advanced prostate cancer' were not included in this review but their citation details were recorded.*

Study objective	Does the study report numerical values for utility or HRQL in terms of the following specific instruments/outcomes:
	• Utilities
	• Utility valuation methods (including those derived using VAS, SG and TTO)
	• Generic preference instruments:
	  – EQ-5D
	  – SF-36
	  – HUI
	  – Disease-specific preference measurements (FACT-P, PORPUS-U)
	• QoL associated with patients undergoing treatment with mitoxantrone either in monotherapy or in combination with any other intervention
	
	NOTE: studies reporting QoL/PRO data in the advanced/metastatic prostate cancer population that do not report the specific items listed above were not included in this review but their citation details were recorded

Caregiver/family	Studies reporting data on the utility or QoL of caregivers or family members of patients diagnosed with prostate cancer were excluded

EQ-5D, EuroQoL Five Dimensions; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HRQL, health-related quality of life; HUI, Health Utilities Index; PORPUS-U, Patient Oriented Prostate Utility Scale; PRO, patient-reported outcome; QoL, quality of life; SF-36, Short Form 36; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

10.12.7 The data abstraction strategy.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded and imported into Excel for screening.

First pass of citations
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.

Second pass of citations
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 data abstraction strategy used was the same as that used in the systematic search of HRQL data in the earlier NICE STA submission for abiraterone acetate for the treatment of mCRPC following previous cytotoxic therapy [61].

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- **Medline**
- **Embase**
- **Medline (R) In-Process**
- **NHS EED**
- **EconLIT.**

Described in section 10.10.1.

10.13.2 The date on which the search was conducted.

Described in section 10.10.2.

10.13.3 The date span of the search.

Described in section 10.10.3.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Described in section 10.10.4.

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Described in section 10.10.5.

10.13.6 The inclusion and exclusion criteria.

The eligibility criteria used for the systematic search of publications on resource utilisation are shown in Table 134.

Table 134: Eligibility criteria used in the systematic review performed for the resource identification, measurement, and valuation systematic review

Exclusion reason	Rationale
Review	Primary economic studies were included in the review and therefore reviews were not required for this study
Animal/in vitro	Only studies in humans were of interest
Children (<18)	An adult population was the focus due to the disease area Therefore, studies in a mixed population of children and adults were only included if subgroup analyses were presented

Study design	Budget impact analyses, resource use studies and cost analyses were included in the review; other economic study designs were excluded
Disease	Only studies of patients diagnosed with prostate cancer were included
Stage of disease	Patients with advanced and/or metastatic prostate cancer were of interest Studies evaluating patients with early stage prostate cancer were excluded Studies of mixed population based on the stage of disease were only included if results for patients with advanced/metastatic prostate cancer were presented
Language/non-English	Only English language studies were included

10.13.7 The data abstraction strategy.

Bibliographic details and abstracts of all citations detected by the literature search were downloaded and imported into the Heron SRDB, a bespoke, SQL-based internet database.

First pass of citations
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.

Second pass of citations
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.

Data extraction
The data presented in the studies still included after the second pass stage were extracted to data extraction grids. This stage was performed by a single reviewer with decisions checked by a second reviewer.

The data abstraction strategy used was the same as that used in the systematic search of HRQL data in the earlier NICE STA submission for abiraterone acetate for the treatment of mCRPC following previous cytotoxic therapy [61].

10.14 Appendix 14: Supplementary results data from the COU-AA-302 study

10.14.1 Secondary outcomes – Kaplan–Meier Curves

[redacted]

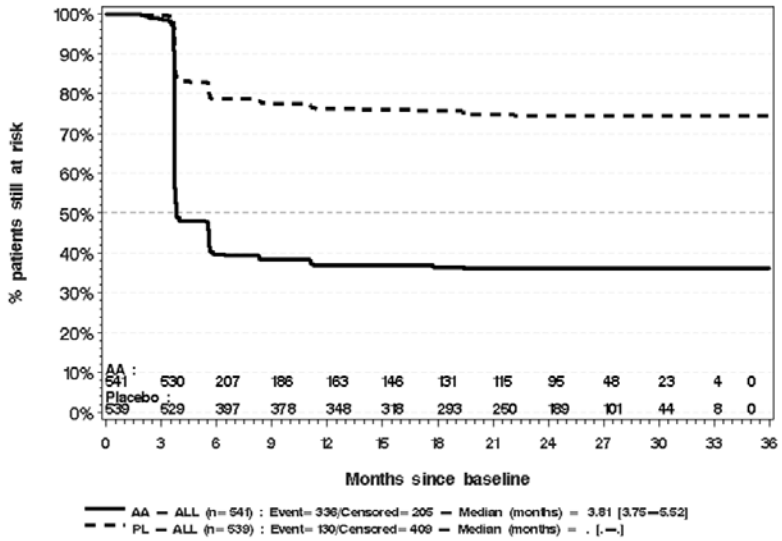
SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference poster [74].
AA, abiraterone acetate plus prednisone; ITT, intent-to-treat; Placebo, placebo plus prednisone.

[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AA, abiraterone acetate plus prednisone; ITT, intent-to-treat; mCRPC, metastatic castration-resistant prostate cancer; Placebo, placebo plus prednisone.

[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AA, abiraterone acetate plus prednisone; PCWG, Prostate Cancer Working Group; Placebo, placebo plus prednisone; PSA, prostate-specific antigen.



[redacted]

SOURCE: Janssen data on file [252]. AA, abiraterone acetate plus prednisone/prednisolone; PL, placebo plus prednisone/prednisolone; Placebo, placebo plus prednisone/prednisolone.

[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AA, abiraterone acetate plus prednisone; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; Placebo, placebo plus prednisone; PS, performance status.

10.14.2 Other outcomes – tables

Table 135: Response to treatment outcomes results – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

Outcome	Median (95% CI) months to outcome		HR (95% CI)	p value
	AAP (N=546)	PP group (N=542)		
PSA response[a]	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed PSA response	[redacted]	[redacted]	[redacted]	[redacted]
Duration of response[b] in subjects with measurable disease at baseline	[redacted]	[redacted]	[redacted]	[redacted]
Objective response rate in subjects with measurable disease at baseline[c]	[redacted]	[redacted]	[redacted]	[redacted]

Data are median (95% CI) or n/N (%).
SOURCE: data on file [253], COU-AA-302 study clinical study report (unpublished) [18].
[a]Confirmed and not confirmed.
[b]By modified RECIST and bone progression criteria.
[c]Proportion of subjects with measurable disease achieving a complete or partial response according to modified RECIST criteria (baseline lymph node size was required to be≥2 cm to be considered a targeted lesion).
AAP, abiraterone acetate plus prednisone/prednisolone; CI, confidence interval; HR, hazard ratio; NR, not reached; PP, placebo plus prednisone; PSA, prostate-specific antigen.

Table 136: Best overall response (confirmed) based on modified RECIST criteria in subjects with measurable disease at baseline (investigator review – ITT population – third interim analysis – 22.05.12, 55% data cut-off)

Best overall response	AAP (N=546)	PP (N=542)
Patients with measurable disease at baseline	[redacted]	[redacted]
Patients with best overall response, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AAP, abiraterone acetate plus prednisone/prednisolone; PP, placebo plus prednisone/prednisolone.

Table 137: Pain-related outcomes results – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

Outcome	Median time to progression in months (95% CI)		HR (95% CI)[a]	p value[b]
	AAP	PP		
Time to progression in				
Average pain intensity[c]	[redacted]	[redacted]	[redacted]	[redacted]
Average pain intensity using 2-point increase threshold (post-hoc analysis)[d]	[redacted]	[redacted]	[redacted]	[redacted]
Worst pain intensity[e]	[redacted]	[redacted]	[redacted]	[redacted]
Worst pain intensity using 2-point increase threshold (post-hoc analysis)[f]	[redacted]	[redacted]	[redacted]	[redacted]
Pain interference[g]	[redacted]	[redacted]	[redacted]	[redacted]
Analgesic use	[redacted]	[redacted]	[redacted]	[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18] and conference abstract [73].
[a]HR is from stratified proportional hazards model. HRs <1 favour AAP.
[b]p value from a log-rank test stratified by ECOG PS grade (0 or 1).
[c]Time from randomisation to the first date the patient experienced a BPI-SF increase by ≥30% from baseline in the average of the BPI-SF pain intensity item scores (#3, #4, #5, #6) that was observed at two consecutive evaluations ≥4 weeks apart without a decrease in analgesic usage score.
[d]Time from randomisation to the first date the patient experienced an increase by 2 points from baseline in the BPI-SF average pain intensity (average of BPI-SF items #3, #4, #5, #6) observed at two consecutive evaluations ≥4 weeks apart without decrease in analgesic usage score.
[e]Time from randomisation to the first date the patient experienced an increase by ≥30% from baseline in the BPI-SF worst pain intensity item (#3) observed at two consecutive evaluations ≥4 weeks apart without a decrease in analgesic usage score.
[f]Time from randomisation to the first date the patient experienced an increase by 2 points from baseline in the BPI-SF worst pain intensity item (#3) observed at two consecutive evaluations ≥4 weeks apart without decrease in analgesic usage score.
[g]Time from randomisation to the first date the patient experienced an increase at any visit in baseline BPI-SF pain interference score of one half the baseline SD of BPI-SF.
AAP, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory short form; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; NE, not estimable; PP, placebo plus prednisone/prednisolone; PS, performance status; SD, standard deviation.

Table 138: Selected subsequent therapy for prostate cancer – ITT population (third interim analysis – 22.05.12, 55% data cut-off)

Subsequent therapy, n (%)	AAP (N=546)	PP (N=542)
Number of subjects with selected subsequent therapy for prostate cancer	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
Ketoconazole	[redacted]	[redacted]
Abiraterone acetate	[redacted]	[redacted]
Sipuleucel-T	[redacted]	[redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AAP, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; PP, placebo plus prednisone/prednisolone.

10.14.3 Other outcomes – Kaplan–Meier Curves

[redacted] 30 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18]
AA, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory short form; ITT, intent-to-treat; Placebo, placebo plus prednisone/prednisolone.

[redacted] 31 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18]
AA, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory short form; ITT, intent-to-treat; Placebo, placebo plus prednisone/prednisolone.

[redacted] 32 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18]
AA, abiraterone acetate plus prednisone/prednisolone; BPI-SF, brief pain inventory short form; ITT, intent-to-treat; Placebo, placebo plus prednisone/prednisolone.

[redacted] 33 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18]
AA, abiraterone acetate plus prednisone/prednisolone; ITT, intent-to-treat; Placebo, placebo plus prednisone/prednisolone.

[redacted] 34 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18]
AA, abiraterone acetate plus prednisone/prednisolone; FACT-P: Functional Assessment of Cancer Therapy – Prostate; ITT, intent-to-treat; Placebo, placebo plus prednisone/prednisolone.

[redacted] 35 [redacted]

SOURCE: COU-AA-302 study clinical study report (unpublished) [18].
AA, abiraterone acetate plus prednisone/prednisolone; FACT-P: Functional Assessment of Cancer Therapy – Prostate; ITT, intent-to-treat; PCS, Prostate Cancer Scale; Placebo, placebo plus prednisone/prednisolone.

[redacted] 36 [redacted]

SOURCE: Reanalysis of existing data.
AA, abiraterone acetate plus prednisone/prednisolone; PL and Placebo, placebo plus prednisone/prednisolone; PSA, prostate-specific antigen.

10.14.4 Supplementary safety data

Table 139: Incidence of AEs of special interest by exposure time (COU-AA-302 study third interim analysis, 55% data cut-off)

	AAP				PP			
	N	**All, %**	**Grade 1–2, %**	**Grade 3–4, %**	**N**	**All, %**	**Grade 1–2, %**	**Grade 3–4, %**
Cardiac disorders								
<3 months	542	6	5	1	540	5	4	1
12–15 months	302	5	3	1	184	8	7	1
≥24 months	154	7	6	1	76	9	9	0
Fatigue								
<3 months	542	19	18	1	540	17	16	1
12–15 months	302	8	7	1	184	8	8	0
≥24 months	154	8	8	0	76	4	4	0
Hyperglycaemia								
<3 months	542	4	2	1	540	4	4	1
12–15 months	302	3	2	0	184	3	2	1
≥24 months	154	1	1	0	76	4	1	3
Hypertension								
<3 months	542	8	7	1	540	8	6	2
12–15 months	302	5	4	1	184	3	2	2
≥24 months	154	2	1	1	76	1	1	0
Osteoporosis								
<3 months	542	1	1	0	540	2	1	0
12–15 months	302	1	0	0	184	2	2	0
≥24 months	154	3	3	0	76	4	4	0
Weight gain								
<3 months	542	2	1	0	540	2	2	0
12–15 months	302	1	1	0	184	0	0	0
≥24 months	154	2	2	0	76	1	1	0

SOURCE: Conference abstract [72].
AAP, abiraterone acetate plus prednisone/prednisolone; PP, placebo plus prednisone/prednisolone.

10.15 Appendix 15: Description of identified studies not directly relevant to the decision problem

Table 140: Summary list of cost-effectiveness evaluations identified in the systematic review

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)
Chopra et al. 2012 [134]	US	CEA, decision-analytical model, payer perspective, no discounting for advanced CRPC patients who previously received docetaxel	Not reported	Incremental QALY versus comparator non specified (probably PP); AA: 0.30	Incremental cost versus comparator non specified (probably PP); AA: $39,320	$129,000
Collins et al., 2007 [101]	UK	CEA, Markov model, NHS perspective, timeframe 15 years, 3.5% discount rate for both costs and health outcomes	Not reported; starting age approx. 68 years	P: 0.81001 M + P: 0.81364 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
Efstathiou 2012 [102]	Greece	CEA, indirect cost-effectiveness model, Third party perspective (Greek healthcare), timeframe not reported, Undiscounted costs were used	Not reported	Not reported	Treatment cost: AA + P + Pl: €25,847 Cabazitaxel + P: €26,648 Treatment cost/incremental month of PFS vs. palliative care AA + P + Pl: €12,924 Cabazitaxel + P: €19,034 Treatment cost/incremental month of OS vs. palliative care AA + P + Pl: €5,619 Cabazitaxel + P: €11,103	Not reported

Joulain 2013 [129]	Sweden	CEA, Markov model, Swedish healthcare	mCRPC patients who progressed after docetaxel	NR	NR	Cabazitaxel + P vs. mitoxantrone + P: SEK 943,270 Cabazitaxel + P vs. P: SEK 990,903
Konski 2004 [106]	US	CUA, Markov model, third party payer/Medicare perspective, timeframe 24 months, no discounting	Hormone-refractory prostate cancer with bone metastases (70 years)	Pain medication: 0.48 SFX RT: 0.51 MFX RT: 0.52 Mitoxantrone + P: 0.41	Incremental cost vs. pain medication ($11,700) SFX RT: $200 MFX RT: $1,500 Mitoxantrone + P: $3,600	vs. pain medication SFX RT: $6,857 MFX RT: $36,000 Mitoxantrone + P: dominated
Ostale 2012 [113]	Spain	CEA, model details not reported, Third party perspective (Spanish NHS), timeframe and discounting details not reported	Not reported	Not reported	Treatment cost difference: Cabazitaxel vs. Mitoxantrone + P: €27,799.93 (range: €13,665.36 to €46,646.01) AA + P vs. Prednisone: €25,386.71 (range: €12,669.65 to €38,103.76)	Not reported
Pereira 2012 [115]	Brazil	CEA/CUA, Markov model, third party perspective (The Brazilian Healthcare system, direct costs only), timeframe not reported, 5% discount rate for costs and outcomes	Not reported	QALY AA + P: 0.7977 Cabazitaxel + P: 0.7329	AA + P: R$79,974 Cabazitaxel + P: R$90,025	AA is the most economically attractive medication

Persson 2012 [116]	Sweden	CUA, survival-based decision analysis model; societal perspective; timeframe and discounting details not reported	Not reported	AA + P: 0.94 Cabazitaxel + P: 0.83	Total cost/patient: AA + P: $103,100 (€74,400) Cabazitaxel + P: $104,600 (€75,500)	Not reported
Pollard 2013 [130]	US	CEA, survival-based decision analysis model; societal perspective; timeframe and discounting details not reported	Not reported	Not reported	CEA with Sipuleucel-T • Placebo (Sipuleucel-T trial): $38,456 • Sipuleucel-T: $144,582 • Sipuleucel-T + D: $165,071 • Sipuleucel-T + D + AA: $227,083 • Sipuleucel-T + D + AA + enzalutamide: $295,474 • Sipuleucel-T + D + AA + enzalutamide + cabazitaxel: $349,767 CEA without Sipuleucel-T • Placebo (D trial): $29,241 • D: $49,729 • D + AA: $111,741 • D + AA + enzalutamide: $180,133 • D + AA + enzalutamide + cabazitaxel: $234,425	Not reported
Soria-Cedillo 2013 [131]	Mexico	BIM, Markov model, institutional, 10 cycles (30 weeks), no discounting	mCRPC patients progressing after docetaxel	NA	861,600 USD (budget impact for public institutions)	NA
Stevenson 2011 [121]	UK	CEA, cohort Markov model constructed in Excel, NHS and personal social services Perspective, timeframe lifetime (14.4 years), 3.5% discount rate for costs and benefits	>18 years (Patient population of TROPIC trial used for economic evaluation)	Cabazitaxel + P/Pl: 1.147 Mitoxantrone + P/Pl: 0.849	Total cost: Cabazitaxel + P/Pl: £35,372 Mitoxantrone + P/Pl: £13,047	Cabazitaxel+ P/Pl vs. Mitoxantrone +P/Pl: £74,938

Wilson 2012 [126]	US	CEA, Decision tree model, societal perspective, timeframe-18 months, undiscounted costs were used	mCRPC after docetaxel	NR	NR	Mitoxantrone vs. placebo: $110,000 AAP vs. mitoxantrone: $76,000 Cabazitaxel + P vs. AAP: $925,000
Yeung 2013 [132]	US	CEA, Markov model, limited societal perspective, lifetime, 3% discount rate, US $	Not reported	Enzalutamide: 1.24 AA: 1.05	Enzalutamide: $84,465 AA: $74,119	$55,070/QALY
Zhong 2012 [133]	US	CUA, decision tree, 18-month timeframe	mCRPC in docetaxel-refractory patients	NR	NR	Mitoxantrone vs. placebo: $110,000 AA vs. mitoxantrone: $76,000 cabazitaxel vs. AA: $925,000
Zhong 2013 [133;136]	US	CEA, decision tree model; societal perspective; 18-month timeframe and discounting details not reported	Not reported	Placebo: 0.43 Mitoxantrone: 0.51 AA: 0.70 Cabazitaxel: 0.76	Placebo: $75,366 Mitoxantrone: $83,171 AA: $101,050 Cabazitaxel: $156,140	Mitoxantrone vs. placebo: $34,677 AA versus placebo: $61,182 Cabazitaxel versus placebo: $400,046

AA, abiraterone acetate; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; D, docetaxel; ICER, incremental cost-effectiveness ratio; M, mitoxantrone; MFX, multifraction; NHS, National Health Service; P, prednisone; Pl, prednisolone; PP, placebo plus prednisone; QALY, quality-adjusted life year; RT, radiotherapy; SFX, single fraction.

Table 141: Summary list of cost-effectiveness evaluations identified from searching of HTA agency publications

Study title	HTA body	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Abiraterone for mCRPC previously treated with a docetaxel-containing regimen [15]	NICE	CUA, survival-based decision model, NHS and personal social services perspective, timeframe 10 years, discounted costs and benefits at 3.5%	Not reported	Not reported	AA+Pl: £2,930 for 120 tablets Prednisolone: £1.03 for a 28-tablet Mitoxantrone+Pl: £200 per 3-week cycle	AA+Pl vs. Pl: £52,851 (for the whole population) AA+Pl vs. Pl: £46,800 (for the patients with one prior chemotherapy, base case)
Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen [45]	NICE	CUA, cohort Markov model, NHS and personal social services perspective, timeframe lifetime (14.4 years), 3.56% for costs and benefits	>65 years	Cabazitaxel +Pl: 0.290 QALY gained	Total incremental cost: Cabazitaxel +Pl: £22,649	£78,016 (European patients with ECOG PS of 0–1, received ≥225 mg/m^2 prior docetaxel therapy) £91,134 (whole population) £87,348 (European patients regardless of ECOG status and prior docetaxel treatment) £86,008 (All TROPIC trial patients with ECOG PS 0 to 1 and received ≥225 mg/m^2 prior docetaxel therapy) Piecewise analysis: £77,765 (European patients with ECOG PS of 0–1, received ≥225 mg/m^2 prior docetaxel therapy) £87,518 (All TROPIC trial patients with ECOG PS 0 to 1 and received ≥225 mg/m^2 prior docetaxel therapy)

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer [147;191]	NICE	Manufacturer's model: CEA, patient level simulation, third party perspective (UK NHS), timeframe and discounting details were not reported	Not reported	Not reported	Not reported	Docetaxel (3-weekly)+P+Pl vs. mitoxantrone+P+Pl: £19,483 per LY gained (base-case results) Docetaxel (3-weekly)+P+Pl vs. mitoxantrone+P+Pl: £30,280 per LY gained (preliminary analysis)
		Assessment committee model: CUA, Markov model, third party perspective (UK NHS), timeframe 15 years, discounting was incorporated however the details were not reported	Not reported	Not reported	Not reported	Docetaxel (3-weekly)+P+Pl vs. mitoxantrone+P+Pl: £32,700 per QALY
Abiraterone acetate 250 mg tablets (Zytiga®) [149]	SMC	CUA, model, perspective, and discounting details were not reported, timeframe 10 years	≥18 years (population of TROPIC trial used for data acquisition)	Not reported	Not reported	Cost per QALY with PAS: AA+Pl vs. Prednisolone/BSC: £46,421 AA+Pl vs. Dexamethasone /BSC: £44,606 AA+Pl vs. Mitoxantrone plus prednisolone: £41,122 AA+Pl vs. Docetaxel retreatment plus prednisolone: £24,205
Cabazitaxel, 60 mg concentrate and solvent for solution for infusion (Jevtana®) [140]	SMC	CUA, Markov model, perspective and discounting details were not reported, timeframe lifetime	≥18 years (population of TROPIC trial used for data acquisition)	Not reported	Not reported	Cabazitaxel+P+Pl vs. Mitoxantrone+Pl: £76,670 (base-case analysis, using only European centre patients with ECOG PS of 0–1, received ≥225 mg/m^2 prior docetaxel therapy) Cabazitaxel+P+Pl vs. Mitoxantrone+Pl: £90,000 (whole population)

Docetaxel concentrate and solvent for solution for infusion, single dose vials (Taxotere®) [148]	SMC	CEA, model, perspective, timeframe, and discounting details were not reported	Not reported	Not reported	Cost per cycle: Docetaxel: £1,023 Mitoxantrone: £169 Cost based on median number of cycles from pivotal trial: Docetaxel: £9,719 (9.5 cycles) Mitoxantrone: £845 (5 cycles) Cost per month: Estramustine: £48 to £480 Cost per year: Estramustine: £576 to £5,760	A median survival gain of 2.40 months at a net cost of £6056, resulting in a cost per additional life year of £30,280 A mean survival gain of 3.73 months at a net cost of £6056, resulting in a cost per additional life year of £19,483
Abiraterone, tablet, 250 mg (as acetate), Zytiga® [142]	PBAC	CUA, decision analytic Markov model, perspective, and discounting details were not reported, timeframe 5 years	Not reported	Not reported	Not reported	The ICERs were between $45,000 and $75,000
Cabazitaxel, injection set containing 1 single use vial concentrate for I.V. infusion, 60 mg (anhydrous) in 1.5 mL with 1 single use vial diluent 4.5 mL, Jevtana® [143]	PBAC	CUA, Q-TWIST analysis of patient-level data	mCRPC post-docetaxel	NR	Aus $10–30 million per year in year 5	The ICERs were between $45,000 and $75,000

Docetaxel, injection set containing 1 single use vial concentrate for I.V. infusion 20 mg (anhydrous)… [144]	PBAC	1) Cohort analysis; 2) CEA; 3) cohort analysis; 4) CUA, survival analysis; 5) CEA/CUA, survival analysis	CRPC	NR	NR	The ICERs were between $45,000 and $75,000
Cabazitaxel, 60 mg concentrate and solvent for solution for infusion (Jevtana®) [140]	SMC	1) CUA, Markov model, lifetime; 2) budget impact, 5 years	mCRPC previously treated with a docetaxel-containing regimen	NR	£36,975 per course	£76,670

AA, abiraterone acetate; BSC, best supportive care; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ECOG, Eastern Cooperative Oncology Group; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LY, life year; mCRPC, metastatic castration-resistant prostate cancer; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PAS, patient access scheme; PBAC, Pharmaceutical Benefits Advisory Committee; Pl, prednisolone; PS, performance status; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium.

10.16 Appendix 16: Additional economic model information

Analysable data set

A total of 902 patients (459 for AAP and 443 for PP) from the COU-AA-302 trial were used in the analysis. A total of 186 patients were excluded due to missing baseline data that were used as predictors (e.g. BPI). In Figure 37 and Figure 38, the blue and green lines are for ITT AAP and ITT PP patients, while the red and brown lines are for analysed AAP and PP patients. Analysis of the 902 patients showed that their times to AAP/BSC (PP) discontinuation and OS are similar to the ITT group. We believe that missing baseline information is missing completely at random and therefore does not bias the results. The majority of patients (85%) followed the pathway of treatments specified in the model; however, the remaining 15% patients who did not follow the treatment pathway (e.g. placebo patients started AAP before docetaxel) were censored at the time they deviated from the pathway.

[redacted]37[redacted]

AA, abiraterone acetate plus prednisolone; Placebo, placebo plus prednisolone; str, strata; TRTP, treatment arm.

[redacted]38[redacted]

AA, abiraterone acetate plus prednisolone; Placebo, placebo plus prednisolone; str, strata; TRTP, treatment arm.

Treatment pathways in the COU-AA-302 trial

The distribution of treatment pathways following by patients in the COU-AA-302 trial AAP and BSC (PP) arms are summarised in Figure 39 and Figure 40, respectively. The pathways included / excluded in the model are denoted in the figures. Among the pathways in the AAP arm, 93% were captured in the model; 91% of pathways in the BSC (PP) were represented in the model. Note that in the statistical analysis, patients who deviated from the trial pathways were censored at the time they deviated.

Figure 39: Treatment pathways in the COU-AA-302 trial AAP arm

	AAP Arm	N	%
Scenarios included in the model	AA -> docetaxel -> Cabazitaxel -> BSC ->Death	20	4%
	AA -> docetaxel -> Cabazitaxel -> BSC(ongoing)	11	2%
	AA -> docetaxel -> Cabazitaxel -> Death	3	1%
	AA -> docetaxel -> Cabazitaxel(ongoing)	11	2%
	AA -> docetaxel -> BSC -> Death	59	11%
	AA -> docetaxel -> BSC(ongoing)	31	6%
	AA -> docetaxel -> Death	23	4%
	AA -> docetaxel(ongoing)	43	8%
	AA -> BSC -> Death	73	13%
	AA -> BSC(ongoing)	93	17%
	AA -> Death	3	1%
	AA -> lost in follow up	4	1%
	Ongoing AA	123	23%
Scenarios not included in the model	AA -> AA retreatment	10	2%
	AA -> Cabazitaxel	4	1%
	AA -> Docetaxel -> AA retreatment	19	3%
	AA -> Docetaxel -> Cabazitaxel -> Docetaxel retreatment	1	0%
	AA -> Docetaxel -> Cabazitaxel -> AA retreatment	7	1%
	AA -> Docetaxel -> Docetaxel retreatment	8	1%
	Sum	**546**	**100%**

AA, abiraterone acetate plus prednisone/prednisolone; BSC, best supportive care.

Figure 40: Treatment pathways in the COU-AA-302 trial BSC (PP) arm

	BSC (PP) Arm	N	%
Scenarios included in the model	Pred -> Docetaxel -> Cabazitaxel -> BSC -> Death	28	5%
	Pred -> Docetaxel -> Cabazitaxel -> BSC(ongoing)	7	1%
	Pred -> Docetaxel -> Cabazitaxel -> Death	1	0%
	Pred -> Docetaxel -> Cabazitaxel(ongoing)	14	3%
	Pred -> Docetaxel -> Abiraterone -> BSC -> Death	5	1%
	Pred -> Docetaxel -> Abiraterone -> BSC(ongoing)	4	1%
	Pred -> Docetaxel -> Abiraterone -> Death	9	2%
	Pred -> Docetaxel -> Abiraterone(ongoing)	21	4%
	Pred -> Docetaxel -> BSC -> Death	87	16%
	Pred -> Docetaxel -> BSC (onging)	44	8%
	Pred -> Docetaxel -> Death	23	4%
	Pred -> Docetaxel(ongoing)	33	6%
	Pred -> BSC -> Death	69	13%
	Pred -> BSC(ongoing)	89	16%
	Pred -> Death	2	0%
	Pred -> lost in follow up	2	0%
	Ongoing Pred	58	11%
Scenarios not included in the model	Pred -> Abiraterone -> BSC -> Death	1	0%
	Pred -> Abiraterone -> BSC (onging)	1	0%
	Pred -> Abiraterone -> Death	1	0%
	Pred -> Abiraterone(ongoing)	12	2%
	Pred -> Docetaxel -> Cabazitaxel -> AA	10	2%
	Pred -> AA -> Docetaxel	1	0%
	Pred -> Cabazitaxel	3	1%
	Pred -> Docetaxel -> AA ->Cabazitaxel	7	1%
	Pred -> Docetaxel -> AA -> Docetaxel retreatment	5	1%
	Pred -> Docetaxel -> Docetaxel retreatment	5	1%
	Sum	**542**	**100%**

AA, abiraterone acetate plus prednisone/prednisolone; BSC, best supportive care; Pred, prednisolone; PP, placebo plus prednisone/prednisolone.

Data for AAP/BSC (PP) survival

- In the COU-AA-302 trial (55% of events data cut), five of the patients who died did so on or before the date of treatment discontinuation. Thus, prediction equations were developed to predict time to death from the time of AAP or BSC (PP) treatment end. Since so few deaths were recorded while on treatment, data did not support development of a competing risk equation for death versus treatment stop. Instead, these deaths were considered in the derivation of OS post-AAP/BSC (PP) treatment discontinuation (with time of death post-AAP/BSC [PP] discontinuation set to 1 day for these five patients). We then tested the OS predicted from the model versus that seen in the trial and were able to closely replicate the trial findings (shown in Figure 41 and Figure 42).

[redacted]

AA, abiraterone acetate plus prednisolone; obs_pred, observed vs. predicted; os, overall survival.

[redacted]

obs_pred, observed vs. predicted; os, overall survival; Placebo, placebo plus prednisolone.

General approach to predictive analyses for time-to-event outcomes

The economic model had to assign times to treatment start and treatment discontinuation for each patient at each line of treatment based on the prior treatments received and other characteristics. This was accomplished with statistical equations that relate these attributes to a time to treatment start/discontinuation distribution from which a specific time can be drawn. Parametric survival analysis techniques were used to identify an appropriate distribution that captured the shape of the hazard of event, and incorporated predictors that can increase or decrease the hazards. More specifically, parametric survival analysis involved the following steps:

1. Observed Kaplan–Meier curves and cumulative hazard functions were examined graphically. If the exploratory analysis indicated that the shape of the cumulative hazard was similar in both treatment arms, then the two arms were modelled together and a treatment indicator was included as a predictor in the model; otherwise, each treatment arm was modelled separately. Next, the parametric distribution was identified. Commonly used distributions such as exponential, Weibull, log-normal, and log-logistic were tested, and the one yielding the closest fit to the observed data was chosen (refer to the Model selection section below for details). Best fitting does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data. To ensure this was not the case, the observed versus predicted distributions by treatment group were examined.
2. Once a parametric distribution was identified, predictors that impacted the risk of progression were tested. This was done by a stepwise approach, where all candidate predictors were first tested on their own to assess whether they were associated with the outcome. A p value of 0.10 was used to decide which variables had a univariate association. Significant predictors were then combined in a multivariate model, which was then manually trimmed to exclude predictors that become non-significant (p>0.1). Predictors were selected based on a 10% level of significance for the following reasons:
    - The p value of 0.10 is often used when the purpose of the analyses is for prediction and not for causal inference [254;255]. The equations derived from COU-AA-302 data were used for predictive purposes
    - Given that these prediction equations were used in the discrete event simulation model (i.e. for each patient we estimated a series of time-to-event predictions), it was very important not to miss any potential predictors that could influence the time-to-event predictions, so it was preferable to be more inclusive. This was especially important in predicting outcomes after docetaxel discontinuation. The number of observed patients receiving treatment following docetaxel was small and the insignificance of the treatment arm as a predictor is due to small sample size and not because the predictor is unimportant.
    - The overarching goal of the analysis was to compare outcomes related to treatment with AAP versus BSC (PP) while also replicating observed OS (key validation measure) from the COU-AA-302 trial. For example,

treatment effect was statistically significant at the 0.10 level (rather than 0.05). Removing AAP treatment effect as a predictor led to an estimated OS curve that deviated from observed OS (we conducted this analysis and shared with the core AAP treatment sequence modelling team and the consensus was that agencies would not trust a model that could not replicate the OS from the trial).

- We considered the clinical relevance of including treatment effect as a predictor versus solely looking at statistical significance.
- In the final equations, two of them included predictors with p>0.1. The first equation was 'Time to AAP/BSC (PP) End'. Baseline BPI #3 0–1 was not a statistically significant predictor but the interaction term (baseline BPI #3 0–1*AA treatment) was, so baseline BPI #3 0–1 was included in the equation. As the baseline BPI #3 0–1 group was a subgroup in the cost-effectiveness analysis, including the interaction term is important to evaluate AAP impact on this subgroup. Also, two survival functions were used in this equation: best fit (log-logistics) function, and Weibull function. To make the prediction consistent when a two-segment approach was used, we kept the predictors the same across the two functions in this equation. The other equation was 'Time from post-docetaxel tx end to death' using 302 trial data. The AA treatment arm was included as a predictor although the p=0.1899. Treatment was included as predictor in this equation for two reasons. Firstly, only 125 patients were included in this analysis as other patients in the 302 trial either had not survived to the end of post-docetaxel treatment or died without post-docetaxel treatment. Among the 125 patients, 71 had died. Secondly, the Kaplan–Meier graph showed that survival in the two treatment groups were different (Figure 38). We believe that the insignificance of the treatment arm as predictor is due to small sample size and the treatment should be included as a predictor in this equation to avoid potential bias. In the final selection of predictors, some continuous variables, such as time spent with previous phase of treatment, were split into categorical variables. These variables were most predicted values from previous lines of treatment (e.g. update age), and may have had extreme values due to the long tail of survival prediction functions, which led to inaccurate OS predictions if the continuous variables were used. Therefore, making them categorical variables improved the accuracy of the model predictions.

3. To check the final models, we primarily focused on comparing observed versus predicted values, as the aim of these was to capture the mechanisms observed in the trial.

The potential predictors were selected among the following: randomised treatment, current age (continuous and categorical), baseline BMI, current ECOG, current BPI (continuous and categorical), baseline analgesic usage score (categorical: 0/1 vs. 2/3), baseline bone metastasis only, current time since diagnosis (years), baseline log (PSA), baseline log (LDH), and baseline log (alkaline phosphatase). To assess whether the effect of treatment on progression was homogeneous across specific subgroups of interest, the following interactions were tested in the time to AAP/BSC (PP) discontinuation analysis: treatment and age, treatment and baseline BPI, treatment and baseline ECOG, and treatment and bone metastasis present at entry.

A p value of 0.2 was used to decide if interactions should remain or be removed from the final model.

For time-to-event equations after discontinuation of AAP/BSC (PP), additional candidate predictors were selected among the following: PSA progression (yes vs. no) at the time of discontinuation of randomised treatment (i.e. AAP or BSC [PP]), radiographic progression (yes vs. no) at the time of discontinuation of randomised treatment, opiate use (yes vs. no) at the time of discontinuation of randomised treatment, and past treatment history (e.g. initial randomised treatment, time on initial randomised treatment, etc.).

As described above, in the model, each patient followed a specific sequence of treatments. Time spent in each period of that sequence was a function of prior treatments and current patient characteristics. While current age and disease duration were updated within DES, other characteristics such as current ECOG status and PSA progression at the time of initial treatment discontinuation were assigned using derived equations that predict how these characteristics vary over time. All analyses were performed using SAS v9.2.

Model selection

The performance of four models (using the exponential, Weibull, log-normal, and log-logistic distribution) for estimating time-to-event outcomes were tested. The AIC and BIC measures, used to assess how well the data was described by alternative models, were computed for each model (see Table 142). AIC and BIC both assess the model fit penalised for the number of parameters in the model. Using a large number of parameters to describe a complex model often improves the fit to the data. Yet, as the number of model parameters approaches the number of data items the amount of information provided by the model decreases. The key variation in the measures is the penalty size (additional parameters carry a greater penalty in BIC), thus the two measures should only disagree when AIC yields a larger model compared to BIC. The distribution giving the smallest criterion value (denoted by bold text in Table 142) was selected as the best-fitting model. Graphs comparing the observed curve to the best-fitting model are shown in Figure 41 and Figure 42. When Weibull is not tested as the best fit, it is added as an alternative function in the model when predicting treatment duration (Time to AAP/BSC [PP] end) as the log-logistics (best fit) function has long tails and may lead to extreme values for treatment duration.

Table 142: Functional fit statistics for prediction equations

Functional Fit Statistic[a]	Distribution			
	Exponential	**Weibull**	**Log-logistic**	**Log-normal**
Time to AAP/BSC (PP) end				
AIC	3,041.561	2,999.362	**2,937.508**	2,939.356
BIC	3,051.535	3,014.322	**2,952.467**	2,954.315
Time from AAP/BSC (PP) end to docetaxel start				
AIC	2,920.323	2,773.02	2,736.841	**2,729.834**
BIC	2,929.930	2,787.43	2,751.252	**2,744.245**
Time from docetaxel start to docetaxel end				
AIC	1,476.469	**1,461.274**	1,535.023	1,672.258
BIC	1,485.048	**1,474.144**	1,547.892	1,685.127
Time from docetaxel end to post-docetaxel treatment start				
AIC	988.185	**987.978**	990.801	995.799
BIC	**996.237**	1,000.056	1,002.879	1,007.877
Time from post-docetaxel treatment start to end				
AIC	**503.936**	504.010	512.445	541.683
BIC	**510.492**	513.845	522.280	551.517
Time from AAP end to death				
AIC	**501.116**	502.132	505.240	519.669
BIC	**505.137**	510.174	513.282	527.711
Time from BSC (PP) end to death				
AIC	**465.442**	467.207	470.876	483.758
BIC	**469.599**	475.521	479.190	492.072
Time from docetaxel start to death				
AIC	311.487	279.746	**277.139**	281.244
BIC	320.066	292.615	**290.009**	294.113
Time from docetaxel end to death				
AIC	702.935	**695.287**	698.581	710.009
BIC	710.908	**707.246**	710.540	721.968
Time from post-docetaxel treatment end to death				
AIC	299.170	299.030	297.331	**296.847**
BIC	**304.827**	307.515	305.816	305.332

AAP, abiraterone acetate plus prednisolone; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BSC, best supportive care; PP, placebo plus prednisolone.
[a]Smaller values imply a better fit.

Prediction equations

The statistical analysis results for estimating times to events (treatment start/end and death) and change in patient characteristics (ECOG, PSA progression, radiographic progression, opiate use) are provided in Table 143 to Table 151 and Table 152 and Table 153, respectively. Additionally, comparisons of observed patient characteristics to the predicted characteristics (in the AAP and BSC [PP] treatment arms) are shown in Table 154.

Time to treatment start/end prediction equations

Table 143: Time to AAP/BSC (PP) end

Distribution	Log-logistic		Weibull	
Parameter	**Estimate**	**p value**	**Estimate**	**p value**
Intercept	6.4295	<0.0001	6.6698	<0.0001
AAP treatment arm	0.4216	0.0001	0.2810	0.0038
Baseline BPI #3 0–1	0.1520	0.1010	0.0434	0.5947
Years from diagnosis to randomisation	0.0274	<0.0001	0.0300	<0.0001
Baseline BMI	0.0138	0.0330	0.0146	0.0139

ECOG=0 at baseline	0.1561	0.0281	0.1133	0.0780
No bone metastasis at baseline	–0.1445	0.0182	–0.1773	0.0013
Log baseline serum PSA (ng/mL)	–0.0984	<0.0001	–0.0787	<0.0001
Log value of haemoglobin at baseline	0.5559	0.0826	0.4415	0.0978
Log value of LDH at baseline (IU/L)	–0.3678	0.0040	–0.2359	0.0498
Log baseline alkaline phosphatase (IU/L)	–0.1565	0.0033	–0.2044	<0.0001
AAP treatment*baseline BPI #3 0–1	0.2076	0.1130	0.2873	0.0143
Scale	0.5012		0.7295	

AAP, abiraterone acetate plus prednisolone; BMI, body mass index; BPI, Brief Pain Inventory; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PP, placebo plus prednisolone; PSA, prostate-specific antigen.

Table 144: Time from AAP/BSC (PP) end to docetaxel start

Distribution	**Log-normal**	
Parameter	**Estimate**	**p value**
Intercept	8.9876	<0.0001
Age at end of AAP/BSC (PP)	0.0344	<0.0001
Years from diagnosis to first-line treatment end <3 years	–0.3942	0.0231
ECOG=0 at AAP/BSC (PP) end	–1.4159	0.0187
ECOG=1 at AAP/BSC (PP) end	–1.6074	0.0069
ECOG=2 at AAP/BSC (PP) end	–1.1962	0.0579
Log baseline serum PSA (ng/mL)	–0.1140	0.0259
PSA progression at AAP/BSC (PP) end	–0.6643	0.0004
Radiographic progression at AAP/BSC (PP) end	–0.4194	0.0058
Opiate use at AAP/BSC (PP) end	–0.4078	0.0117
Log value of LDH at baseline (IU/L)	–0.5043	0.0725
Log baseline alkaline phosphatase (IU/L)	–0.2053	0.0901
Days from AAP/BSC (PP) start to end 0–91	–0.6774	0.0089
Days from AAP/BSC (PP) start to end 92–274	–0.1282	0.4514
Days from AAP/BSC (PP) start to end 275–365	–0.0824	0.6953
Scale	1.8229	

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PP, placebo plus prednisolone; PSA, prostate-specific antigen.

Table 145: Time from docetaxel start to docetaxel end

Distribution	**Weibull**	
Parameter	**Estimate**	**p value**
Intercept	5.2400	<0.0001
Scale	0.8426	

Table 146: Time from docetaxel end to post-docetaxel treatment start

Distribution	**Weibull**	
Parameter	**Estimate**	**p value**
Intercept	4.0919	<0.0001
AAP treatment arm	–0.3999	0.0101
Age at end of docetaxel treatment	0.0370	<0.0001
ECOG=0 at docetaxel end	–0.6813	0.0177
ECOG=1 at docetaxel end	–0.4991	0.0698
Baseline analgesic use level in last 24 hours	0.3746	0.0169
Days from docetaxel start to end	–0.0034	<0.0001
Scale	1.0387	

AAP, abiraterone acetate plus prednisolone; ECOG, Eastern Cooperative Oncology Group.

Table 147: Time from post-docetaxel treatment start to end

Distribution	Weibull	
Parameter	**Estimate**	**p value**
Intercept	5.2241	<0.0001
AAP treatment arm	–0.4086	0.0164
Scale	0.8717	

AAP, abiraterone acetate plus prednisolone.

Survival prediction equations

Table 148: Time from AAP/BSC (PP) end to death by treatment arm

Distribution	Weibull[a]	
Parameter	**Estimate**	**p value**
AAP arm		
Intercept	9.7037	<0.0001
Age <65 years at AAP end	1.5186	0.0037
Age 65–75 years at AAP end	0.6239	0.0170
ECOG=0 at AAP end	0.7673	0.0070
Radiographic progression at AAP end	–0.9477	<0.0001
Log baseline serum PSA (ng/mL)	–0.3076	0.0002
Opiate use at AAP end	–0.6162	0.0097
Log baseline alkaline phosphatase (IU/L)	–0.3806	0.0187
Scale	0.9444	
BSC (PP) arm		
Intercept	13.1193	<0.0001
Age 40–59 at BSC (PP) end	2.1579	0.0205
Age 60–69 at BSC (PP) end	1.3015	0.0008
Age 70–79 at BSC (PP) end	0.9097	0.0071
Age 80–84 at BSC (PP) end	0.7597	0.0243
ECOG=0 at BSC (PP) end	1.3328	0.0021
ECOG=1 at BSC (PP) end	0.9190	0.0238
ECOG=2 at BSC (PP) end	0.5173	0.2638
Log baseline serum PSA (ng/mL)	–0.2110	0.0086
Opiate use at BSC (PP) end	–0.6336	0.0093
Log value of LDH at baseline	–1.3972	0.0013
Scale	0.8562	

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PP, placebo plus prednisolone; PSA, prostate-specific antigen.
[a]The Weibull distribution was used for both the AAP and BSC (PP) treatment arms.

Table 149: Time from docetaxel start to death

Distribution	Log-logistic	
Parameter	**Estimate**	**p value**
Intercept	10.2560	<0.0001
AAP treatment arm	–0.3142	0.0212
Years from diagnosis to docetaxel start	0.0575	0.0039
ECOG=0 at docetaxel start	0.5795	0.0029
ECOG=1 at docetaxel start	0.5270	0.0033
No bone metastasis at baseline	–0.4431	0.0044
Radiographic progression at AAP/BSC (PP) end	–0.4000	0.0180
Time from AAP/BSC (PP) end to docetaxel start	–0.0018	0.0020
Log value of LDH at baseline	–0.7621	0.0017
Scale	0.3780	

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PP, placebo plus prednisolone.

Table 150: Time from docetaxel end to death

Distribution	Weibull	
Parameter	**Estimate**	**p value**
Intercept	5.2099	<0.0001
AAP treatment arm	–0.2700	0.0496
ECOG=0 at docetaxel end	1.2002	0.0006
ECOG=1 at docetaxel end	0.7704	0.0152
ECOG=2 at docetaxel end	0.4477	0.1899
Scale	0.7980	

AAP, abiraterone acetate plus prednisolone; ECOG, Eastern Cooperative Oncology Group.

Table 151: Time from post-docetaxel treatment end to death

Distribution	Weibull	
Parameter	**Estimate**	**p value**
Intercept	7.1534	<0.0001
AAP treatment arm	0.2581	0.1899
Age at post-docetaxel treatment end	–0.0268	0.0262
Years to diagnosis <3	–0.9538	0.0005
Scale	0.8123	

AAP, abiraterone acetate plus prednisolone.

Patient disease characteristics prediction equations

Table 152: ECOG score

Parameter	Estimate	p value
ECOG at discontinuation of AAP/BSC (PP)[a]		
Intercept 0	5.9818	<0.0001
Intercept 1	8.6005	<0.0001
Intercept 2	10.2291	<0.0001
Time from AAP/BSC (PP) start to end	–0.0008	0.0102
Baseline BMI	–0.0304	0.0504
Baseline age	–0.0594	<0.0001
Log baseline alkaline phosphatase (IU/L)	–0.4029	0.0001
ECOG=0 at baseline	1.4716	<0.0001
ECOG at start of docetaxel[a]		
Intercept 0	–0.8594	0.4675
Intercept 1	2.7006	0.0230
Time from AAP/BSC (PP) end to docetaxel start	–0.0040	<0.0001
Age at docetaxel start	–0.0197	0.0892
Baseline BMI	–0.0709	0.0009
ECOG=0 at AAP/BSC (PP) end	5.1093	<0.0001
ECOG=1 at AAP/BSC (PP) end	2.8751	<0.0001
ECOG at docetaxel discontinuation[a]		
Intercept 0	–3.1149	0.0006
Intercept 1	0.6645	0.4587
Intercept 2	2.4817	0.0066
Days from AAP/BSC (PP) start to end ≤183	–0.4633	0.5800
Days from AAP/BSC (PP) start to end 184–548	0.0156	0.9851
Days from AAP/BSC (PP) start to end 549–731	0.4274	0.6451
Log baseline serum PSA (ng/mL)	–0.1488	0.0307
ECOG=0 at docetaxel start	4.4290	<.0001
ECOG=1 at docetaxel start	1.6834	<.0001
ECOG at start of post-docetaxel treatment[a]		
Intercept 0	–3.2027	0.0003
Intercept 1	1.0946	0.1956
Days from docetaxel end to post-docetaxel treatment start	–0.0032	0.0535
Log baseline serum PSA (ng/mL)	–0.3458	0.0035
Baseline BPI #3 0–1	0.7229	0.0473

Parameter	Estimate	p value
ECOG=0 at docetaxel end	4.6580	<0.0001
ECOG=1 at docetaxel end	2.5147	0.0004

AAP, abiraterone acetate plus prednisolone; BMI, body mass index; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; PP, placebo plus prednisolone; PSA, prostate-specific antigen.
[a]Estimated using the cumulative logit distribution.

Table 153: PSA progression, radiographic progression and opiate use at AAP/BSC (PP) end

Parameter	Estimate	p value
PSA progression[a]		
Intercept	1.59200	0.0149
AAP treatment arm	–0.4442	0.0091
Time from AAP/BSC (PP) start to end	0.00533	<0.0001
Baseline age	–0.02530	0.0052
Radiographic progression[a]		
Intercept	–0.59640	0.0028
AAP treatment arm	–0.36000	0.0199
Time from AAP/BSC (PP) start to end	0.00103	0.0079
Baseline age <65 years	0.34100	0.0518
PSA progression at AAP/BSC (PP) end	0.79240	<0.0001
No bone metastasis at baseline	0.83110	<0.0001
Opiate use[a]		
Intercept	–2.22530	0.0305
Baseline BMI	0.04480	0.0145
Days from diagnosis to randomisation	–0.00012	0.0254
Log baseline alkaline phosphatase (IU/L)	0.29630	0.0181
Baseline analgesic use level in last 24 hours of 0	–1.25070	0.0182
Baseline analgesic use level in last 24 hours of 1	–0.63570	0.2330
Baseline BPI #3 0–1	–0.42550	0.0269

AAP, abiraterone acetate plus prednisolone; BMI, body mass index; BPI, Brief Pain Inventory; BSC, best supportive care; PP, placebo plus prednisolone; PSA, prostate-specific antigen.
[a]Estimated using the binary logit distribution.

Table 154: Comparison of observed and predicted patient characteristics

Parameter	Observed	Predicted	
		AAP	BSC (PP)
ECOG at discontinuation of AAP/BSC (PP), %			
0	47.29	43.60	48.27
1	41.65	42.27	40.63
2	8.47	10.17	8.45
3	2.59	3.96	2.65
ECOG at start of docetaxel, %			
0	36.40	35.01	36.04
1	50.88	50.31	49.61
2	12.72	14.69	14.35
ECOG at docetaxel discontinuation, %			
0	28.63	32.75	31.30
1	55.21	55.15	54.84
2	12.27	9.32	10.58
3	3.89	2.78	3.28
ECOG at start of post-docetaxel treatment, %			
0	30.23	32.52	29.15
1	59.88	59.01	59.88
2	9.88	8.47	10.97

PSA progression, %	73.36	80.18	76.30
Radiographic progression, %	66.09	68.13	69.86
Opiate use, %	25.26	24.70	24.70

AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; PP, placebo plus prednisolone; PSA, prostate-specific antigen.

Implementation of prediction equations

Time-to-event estimation

The prediction equations were used in the simulation model to estimate time to treatment start, time to treatment discontinuation, and time to death. The event times (T_i) for individual patients were random variables corresponding to a continuous probability distribution (exponential, Weibull, log-logistic, or log-normal). For example, for all possible times to first-line treatment discontinuation (T_i) after baseline, there was a particular probability (corresponding to the Weibull distribution, see Table 155) that the patient will end first-line treatment at exactly time T_i. To assign the patient an event/survival time, the simulation first computed the adjusted intercept by taking the intercept plus the sumproduct of the parameter estimates and the patient characteristics corresponding to the parameters. Then, the simulation generated a random number (RND) uniformly distributed between 0 and 1 (RNDa) and transformed this number into a random variate from a specified distribution. The uniformly distributed random number was transformed to another distribution (e.g. Weibull) by applying the appropriate equation in Table 155.

Table 155: Parametric survival distributions

Distribution	Function
Weibull	(-LN(RNDa)/EXP(-adjusted intercept/scale))^scale
Log-logistic	((1/RNDa-1)/EXP(-adjusted intercept/scale))^scale
Log-normal	EXP(NORMINV(1-RNDa,adjusted intercept,scale))
Exponential	-LN(RNDa)/EXP(-adjusted intercept))

Updating ECOG

ECOG was updated at four time points (first-line treatment end, start of docetaxel, end of docetaxel, start of third-line treatment) in the simulation model using a cumulative logit model to estimate the cumulative probability of being at or above a given ECOG score. We defined the cumulative probability by letting $P(y \leq n)$ represent the probability that the ordinal response variable (y) lay in category n or below (i.e. in category 1, 2, …, or n). For an n-category response, we had n cumulative probabilities where $P(y \leq 1) \leq P(y \leq 2) \leq \ldots \leq P(y \leq n)=1$. For instance, if there were four response categories for ECOG (e.g. scores of 0, 1, 2, 3) then the cumulative probabilities were given by P(ECOG=0) and P(ECOG≤1)=P(ECOG=0)+P(ECOG=1) and P(ECOG≤2)=P(ECOG=0)+P(ECOG=1)+P(ECOG=2) and P(ECOG≤3)=1 (the probabilities must sum to 1).

The effect of the explanatory variables on all of the cumulative probabilities are described by the cumulative logit model. A distinct intercept parameter ($\alpha_0, \alpha_1, \alpha_2$) was estimated for each cumulative probability (α_j increases with j=0, 1, 2). For each cumulative probability, the model was described by (Equation 3) where α_j represents the intercept for each response category j, n represents the number of response categories, m denotes the number of explanatory variables, and β represents the coefficients of the explanatory variables.

$$\text{logit}[P(ECOG \leq j)]=\alpha_j - \beta_1 + \beta_2 + \beta_3 + \ldots + \beta_m;\ j=1, 2, \ldots, n-1 \qquad \text{(Equation 3)}$$

For example, if there were four possible ECOG scores of 0, 1, 2, 3 (n=4), then the model described three relationships: (1) the effect of the explanatory variables on the likelihood that ECOG≤0, (2) the effect of the explanatory variables on the likelihood that ECOG≤1, and (3) the effect of the explanatory variables on the likelihood that ECOG≤2.

In the simulation model, logits of the cumulative probabilities were estimated by taking each intercept plus the sumproduct of the parameter estimates and corresponding individual patient characteristics. The logits were then transformed to a cumulative probability (i.e. value from 0 to 1) using the logit link function as shown by (Equation 4). A random number uniformly distributed between 0 and 1 (RNDb) was then selected and we used the estimated cumulative probability distribution to allocate RNDb to the new ECOG value (i.e. determine which category RNDb fell in).

P(ECOG≤j)=EXP(logit[P(ECOG≤j)])/(1 + EXP(logit[P(ECOG≤j)])) (Equation 4)

Estimating risk of PSA progression, radiographic progression, and opiate use
Risk of PSA progression, radiographic progression, and opiate use at the end of first-line treatment were estimated using binary logit models. The models used the explanatory variables as described in Equation 5 where α is the intercept and the β coefficients correspond to m parameters. Each nonlinear equation describes the relative effect of each predictor on the patient's risk of PSA progression, radiographic progression, and opiate use. The response was predicted by adding the intercept to the sumproduct of the parameter estimates and the values of the individual patient characteristics in the simulation model. The response was then transformed into an individual probability (p_i) of PSA progression/radiographic progression/opiate use (i.e. a value between 0 and 1) using the logit link function (rearranging Equation 5 to solve for p_i) as shown by Equation 6. A random number was generate by sampling from a Uniform distribution ranging from 0 to 1 [RNDc ~ UNIF(0,1)] and RNDc was compared to the estimated probability (p_i). RNDc values falling below p_i mean that the patient does experience PSA progression/radiographic progression/opiate use at first-line treatment discontinuation.

$$\text{logit}(p_i)=\ln\left(\frac{p_i}{1-p_i}\right)=\alpha+\beta_1+\beta_2+\beta_3+\ldots+\beta_m \quad \text{(Equation 5)}$$

$$p_i=\text{EXP}(\text{logit}[p_i])/(1+\text{EXP}(\text{logit}[p_i])) \quad \text{(Equation 6)}$$

Covariance matrices for Cholesky decomposition

Table 156: Time to first-line treatment discontinuation (option A)

Panel A

	Intercept	TRTP AA	BLBPICAT01	DIAG2RANYRS	BMI	BLECOGCAT0	BNMETNo
Intercept	1.25	–0.0151	–0.00627	–0.000913	–0.00114	–0.00346	–0.00495
TRTPAA	–0.0151	0.0123	0.00585	–0.00000895	0.000000726	–0.0000309	0.000455
BLBPICAT0N1	–0.00627	0.00585	0.00859	–0.0000213	0.0000028	–0.000724	0.000326
DIAG2RANYRS	–0.000913	–0.00000895	–0.0000213	0.0000391	0.00000204	0.0000442	–0.00000571
BMI	–0.00114	0.000000726	0.0000028	0.00000204	0.0000419	0.0000121	–0.0000137
BLECOGCAT0	–0.00346	–0.0000309	–0.000724	0.0000442	0.0000121	0.00506	–0.0000603
BNMETNo	–0.00495	0.000455	0.000326	–0.00000571	–0.0000137	–0.0000603	0.00375
LOG_PSABL	–0.00112	–0.0000714	–0.000103	–0.0000105	0.00000891	0.0000888	–0.000269
LOG_HGBBL	–0.288	0.00307	–0.000941	0.0000405	–0.0000376	–0.00138	0.00161
LOG_LDHBL	–0.0854	0.000227	0.000211	0.0000781	–0.0000202	0.000466	–0.000536
LOG_ALKPBL	–0.00302	0.0000689	0.000506	0.0000255	0.0000183	0.0000575	0.00061
TRTPAA*BLBPICAT01	0.0173	–0.0123	–0.00835	–0.00000196	0.00000113	0.000016	–0.000675
Scale	0.00013	–0.0000108	–0.00000211	0.000000763	–0.000000339	–0.0000125	–0.000014

Panel B

	LOG_PSABL	LOG_HGBBL	LOG_LDHBL	LOG_ALKPBL	TRTPAA*BLBPICAT01	Scale
Intercept	–0.00112	–0.288	–0.0854	–0.00302	0.0173	0.00013
TRTPAA	–0.0000714	0.00307	0.000227	0.0000689	–0.0123	–0.0000108
BLBPICAT0N1	–0.000103	–0.000941	0.000211	0.000506	–0.00835	–0.00000211
DIAG2RANYRS	–0.0000105	0.0000405	0.0000781	0.0000255	–0.00000196	0.000000763
BMI	0.00000891	–0.0000376	–0.0000202	0.0000183	0.00000113	–0.000000339
BLECOGCAT0	0.0000888	–0.00138	0.000466	0.0000575	0.000016	–0.0000125
BNMETNo	–0.000269	0.00161	–0.000536	0.00061	–0.000675	–0.000014
LOG_PSABL	0.000474	0.000587	–0.0000894	–0.00037	0.0000755	–0.00000564
LOG_HGBBL	0.000587	0.103	0.00415	0.000626	–0.00355	0.0000303
LOG_LDHBL	–0.0000894	0.00415	0.0163	–0.00226	–0.000314	–0.0000232
LOG_ALKPBL	–0.00037	0.000626	–0.00226	0.00284	–0.000144	–0.0000059
TRTPAA *BLBPICAT01	0.0000755	–0.00355	–0.000314	–0.000144	0.0172	0.0000432
Scale	–0.00000564	0.0000303	–0.0000232	–0.0000059	0.0000432	0.000235

TRTPAA, abiraterone plus prednisolone treatment arm; BLBPICAT0N1, baseline Brief Pain Inventory 0–1; DIAG2RANYRS, years from diagnosis to randomisation; BMI, baseline body mass index; BLECOGCAT0, ECOG=0 at baseline; BNMETNo, no bone metastasis at baseline; LOG_PSABL: log baseline

serum PSA (ng/mL); LOG_HGBBL, log value of haemoglobin at baseline; LOG_LDHBL, log value of lactate dehydrogenase at baseline; LOG_ALKPBL, log baseline alkaline phosphatase (IU/L); TRTPAA*BLBPICAT0N1, interaction between variables TRTPAA and BLBPICAT0N1.

Table 157: Time to First Line Treatment Discontinuation (Option B)

Panel A							
	Intercept	**TRTPAA**	**BLBPICAT0N1**	**DIAG2RANYRS**	**BMI**	**BLECOGCAT0**	**BNMETNo**
Intercept	1.06	–0.0123	–0.00762	–0.000607	–0.000915	–0.000503	–0.00213
TRTPAA	–0.0123	0.00945	0.00437	0.00000435	0.0000189	0.000000479	0.000181
BLBPICAT0N1	–0.00762	0.00437	0.00666	–0.0000437	–0.00000396	–0.000542	0.000367
DIAG2RANYRS	–0.000607	0.00000435	–0.0000437	0.0000357	0.00000302	0.000055	0.00000153
BMI	–0.000915	0.0000189	–0.00000396	0.00000302	0.0000354	0.0000161	–0.0000346
BLECOGCAT0	–0.000503	0.000000479	–0.000542	0.000055	0.0000161	0.00413	0.000112
BNMETNo	–0.00213	0.000181	0.000367	0.00000153	–0.0000346	0.000112	0.00306
LOG_PSABL	–0.00154	0.0000849	0.000186	–0.0000103	0.0000089	–0.0000549	–0.000156
LOG_HGBBL	–0.224	0.00227	0.00025	–0.0000136	–0.0000364	–0.00119	0.0000373
LOG_LDHBL	–0.0851	0.000411	0.000289	0.0000512	–0.0000233	–0.000202	0.000111
LOG_ALKPBL	0.000788	–0.000224	0.000167	0.0000166	0.0000117	0.000243	0.000221
TRTPAA*BLBPICAT01	0.0132	–0.00944	–0.00642	0.0000143	–0.000000613	0.0000871	–0.000366
Scale	–0.000198	0.0000882	0.0000405	0.00000721	0.00000216	0.000043	–0.0000428

Panel B						
	LOG_PSABL	**LOG_HGBBL**	**LOG_LDHBL**	**LOG_ALKPBL**	**TRTPAA*BLBPICAT01**	**Scale**
Intercept	–0.00154	–0.224	–0.0851	0.000788	0.0132	–0.000198
TRTPAA	0.0000849	0.00227	0.000411	–0.000224	–0.00944	0.0000882
BLBPICAT0N1	0.000186	0.00025	0.000289	0.000167	–0.00642	0.0000405
DIAG2RANYRS	–0.0000103	–0.0000136	0.0000512	0.0000166	0.0000143	0.00000721
BMI	0.0000089	–0.0000364	–0.0000233	0.0000117	–0.000000613	0.00000216
BLECOGCAT0	–0.0000549	–0.00119	–0.000202	0.000243	0.0000871	0.000043
BNMETNo	–0.000156	0.0000373	0.000111	0.000221	–0.000366	–0.0000428
LOG_PSABL	0.00036	0.00085	–0.00022	–0.000218	–0.000194	–0.000028
LOG_HGBBL	0.00085	0.0711	0.00775	–0.0000236	–0.00261	0.000181
LOG_LDHBL	–0.00022	0.00775	0.0145	–0.00205	–0.000466	–0.0000683
LOG_ALKPBL	–0.000218	–0.0000236	–0.00205	0.00214	0.000235	–0.0000186
TRTPAA*BLBPICAT01	–0.000194	–0.00261	–0.000466	0.000235	0.0137	0.0000909
Scale	–0.000028	0.000181	–0.0000683	–0.0000186	0.0000909	0.00047

TRTPAA, abiraterone acetate plus prednisolone treatment arm; BLBPICAT0N1, baseline Brief Pain Inventory 0–1; DIAG2RANYRS, years from diagnosis to randomisation; BMI, baseline body mass index; BLECOGCAT0, ECOG=0 at baseline; BNMETNo, no bone metastasis at baseline; LOG_PSABL, log baseline serum prostate–specific antigen (ng/mL); LOG_HGBBL, log value of haemoglobin at baseline; LOG_LDHBL, log value of lactate dehydrogenase at baseline; LOG_ALKPBL, log baseline alkaline phosphatase (IU/L); TRTPAA*BLBPICAT0N1, interaction between variables TRTPAA and BLBPICAT0N1.

Table 158: Time to docetaxel

Panel A

	Intercept	**NEWAGE**	**NEWDIAG2RANYRSCAT20__3_yrs**	**ECOGDISC1CAT0**	**ECOGDISC1CAT1**	**ECOGDISC1CAT2**	**LOG_PSABL**	**PSA_PROG_YN**
Intercept	2.68	–0.00576	0.000453	–0.435	–0.392	–0.362	0.00196	–0.0314
NEWAGE	–0.00576	0.0000713	0.000347	0.000649	0.000345	0.000203	–0.00003	0.000135
NEWDIAG2RANYRSCAT20__3_yrs	0.000453	0.000347	0.0301	–0.000537	–0.00184	–0.00149	0.000357	0.00234
ECOGDISC1CAT0	–0.435	0.000649	–0.000537	0.362	0.347	0.343	0.00185	0.000106
ECOGDISC1CAT1	–0.392	0.000345	–0.00184	0.347	0.354	0.34	0.0015	–0.00186
ECOGDISC1CAT2	–0.362	0.000203	–0.00149	0.343	0.34	0.398	0.00116	–0.000968
LOG_PSABL	0.00196	–0.00003	0.000357	0.00185	0.0015	0.00116	0.00262	–0.000591
PSA_PROG_YN	–0.0314	0.000135	0.00234	0.000106	–0.00186	–0.000968	–0.000591	0.0352
RAD_PROG_YN	–0.0154	0.0000405	–0.0000668	–0.00135	0.000167	0.00158	–0.0000831	–0.00378
OPI_USE_YN	–0.0338	0.000132	–0.00191	0.014	0.00823	0.00692	0.000298	–0.000102
LOG_LDHBL	–0.348	–0.0000179	–0.00488	0.00224	0.000308	–0.002	–0.000468	–0.000423
LOG_ALKPBL	0.0016	0.0000412	–0.000929	0.00325	0.00284	0.00163	–0.00172	–0.000664
TTDISC1CAT20–91	–0.000139	0.0000672	–0.00407	–0.00154	–0.0000864	0.00209	–0.00181	0.0208
TTDISC1CAT292–274	–0.0076	0.0000795	–0.00493	0.0025	0.00213	0.00373	–0.000841	0.00542
TTDISC1CAT2275–365	–0.0174	0.0000414	–0.00444	0.0048	0.00443	0.00342	–0.000284	0.000683
Scale	0.0018	0.0000442	–0.000164	–0.00274	–0.00264	–0.00212	–0.0000175	–0.000606

Panel B

	RAD_PROG_YN	**OPI_USE_YN**	**LOG_LDHBL**	**LOG_ALKPBL**	**TTDISC1CAT20-91**	**TTDISC1CAT292-274**	**TTDISC1CAT2275-365**	**Scale**
Intercept	–0.0154	–0.0338	–0.348	0.0016	–0.000139	–0.0076	–0.0174	0.0018
NEWAGE	0.0000405	0.000132	–0.0000179	0.0000412	0.0000672	0.0000795	0.0000414	0.0000442
NEWDIAG2RANYRSCAT20__3_yrs	–0.0000668	–0.00191	–0.00488	–0.000929	–0.00407	–0.00493	–0.00444	–0.000164

ECOGDISC1CAT0	–0.00135	0.014	0.00224	0.00325	–0.00154	0.0025	0.0048	–0.00274
ECOGDISC1CAT1	0.000167	0.00823	0.000308	0.00284	–0.0000864	0.00213	0.00443	–0.00264
ECOGDISC1CAT2	0.00158	0.00692	–0.002	0.00163	0.00209	0.00373	0.00342	–0.00212
LOG_PSABL	–0.0000831	0.000298	–0.000468	–0.00172	–0.00181	–0.000841	–0.000284	–0.0000175
PSA_PROG_YN	–0.00378	–0.000102	–0.000423	–0.000664	0.0208	0.00542	0.000683	–0.000606
RAD_PROG_YN	0.0231	0.00111	–0.000742	0.000705	0.00664	–0.0000897	0.00117	–0.000297
OPI_USE_YN	0.00111	0.0261	0.00277	–0.00219	0.000435	0.00149	0.0022	–0.000146
LOG_LDHBL	–0.000742	0.00277	0.0788	–0.0132	–0.00617	–0.00364	–0.000478	0.000167
LOG_ALKPBL	0.000705	–0.00219	–0.0132	0.0147	–0.000802	0.000444	–0.000599	–0.00017
TTDISC1CAT20–91	0.00664	0.000435	–0.00617	–0.000802	0.0671	0.0198	0.0166	–0.000782
TTDISC1CAT292–274	–0.0000897	0.00149	–0.00364	0.000444	0.0198	0.029	0.0158	–0.00066
TTDISC1CAT2275-365	0.00117	0.0022	–0.000478	–0.000599	0.0166	0.0158	0.0442	–0.000536
Scale	–0.000297	–0.000146	0.000167	–0.00017	–0.000782	–0.00066	–0.000536	0.00343

NEWAGE, age at end of abiraterone acetate plus prednisolone/best supportive care – placebo plus prednisolone (AAP/BSC [PP]); NEWDIAG2RANYRSCAT20__3_yrs, years from diagnosis to first-line treatment end <3 years; ECOGDISC1CAT0, ECOG=0 at AAP/BSC (PP) end; ECOGDISC1CAT1, ECOG=1 at AAP/BSC (PP) end; ECOGDISC1CAT2, ECOG=2 at AAP/BSC (PP) end; LOG_PSABL, log baseline serum prostate specific antigen (PSA) (ng/mL); PSA_PROG_YN, PSA progression at AAP/BSC (PP) end; RAD_PROG_YN, radiographic progression at AAP/BSC (PP) end; OPI_USE_YN, opiate use at AAP/BSC (PP) end; LOG_LDHBL, log value of lactate dehydrogenase at baseline; LOG_ALKPBL, log baseline alkaline phosphatase (IU/L); TTDISC1CAT20N91, days from AAP/BSC (PP) start to end 0–91; TTDISC1CAT292N274, days from AAP/BSC (PP) start to end 92–274; TTDISC1CAT2275N365, days from AAP/BSC (PP) start to end 275–365.

Table 159: Time to docetaxel discontinuation

	Intercept	**Scale**
Intercept	0.00171	–0.0000942
Scale	–0.0000942	0.00114

Table 160: Time to death while on docetaxel

	Intercept	**TRTPAA**	**NEWDIAG2RANYRS**	**ECOGSTDOXICAT0**	**ECOGSTDOXICAT1**	**BNMETNo**	**RAD_PROG_YN**	**TTDOX**	**LOG_LDHBL**	**Scale**
Intercept	1.89	–0.00716	–0.00194	–0.0128	–0.0022	–0.0487	–0.049	–0.000173	–0.329	0.0127
TRTPAA	–0.00716	0.0186	–0.000195	–0.0027	–0.00133	0.00106	–0.000619	0.00000185	–0.000216	–0.000656
NEWDIAG2RANYRS	–0.00194	–0.000195	0.000398	0.00031	0.0000623	–0.000361	–0.000419	–0.00000212	0.000147	0.000123
ECOGSTDOXICAT0	–0.0128	–0.0027	0.00031	0.0378	0.0228	–0.00165	–0.00375	0.00000484	–0.000966	0.00107

ECOGSTDOXICAT1	–0.0022	–0.00133	0.0000623	0.0228	0.0322	–0.00209	–0.00172	–0.0000019	–0.00302	0.000553
BNMETNo	–0.0487	0.00106	–0.000361	–0.00165	–0.00209	0.0242	–0.00309	0.00000637	0.00648	–0.000945
RAD_PROG_YN	–0.049	–0.000619	–0.000419	–0.00375	–0.00172	–0.00309	0.0286	–0.00000312	0.00624	–0.000389
TTDOX	–0.000173	0.00000185	–0.00000212	0.00000484	–0.0000019	0.00000637	–0.00000312	0.00000035	0.0000264	–0.00000174
LOG_LDHBL	–0.329	–0.000216	0.000147	–0.000966	–0.00302	0.00648	0.00624	0.0000264	0.059	–0.00182
Scale	0.0127	–0.000656	0.000123	0.00107	0.000553	–0.000945	–0.000389	–0.00000174	–0.00182	0.00167

TRTPAA, abiraterone acetate plus prednisolone (AAP) treatment arm; NEWDIAG2RANYRS, years from diagnosis to docetaxel start; ECOGSTDOXICAT0, ECOG=0 at docetaxel start; ECOGSTDOXICAT1, ECOG=1 at docetaxel start; BNMETNo, no bone metastasis at baseline; RAD_PROG_YN, radiographic progression at AAP/best supportive care – corticosteroids (BSC [PP]) end; TTDOX, time from AAP/BSC (PP) end to docetaxel start; LOG_LDHBL, log value of lactate dehydrogenase at baseline.

Table 161: Time to death after docetaxel

	Intercept	**TRTPAA**	**ECOGENDDOXICAT0**	**ECOGENDDOXICAT1**	**ECOGENDDOXICAT2**	**Scale**
Intercept	0.0992	–0.0125	–0.0947	–0.0938	–0.0964	–0.000299
TRTPAA	–0.0125	0.0189	0.00492	0.00388	0.008	–0.000223
ECOGENDDOXICAT0	–0.0947	0.00492	0.121	0.0943	0.0941	0.00308
ECOGENDDOXICAT1	–0.0938	0.00388	0.0943	0.101	0.0933	0.00192
ECOGENDDOXICAT2	–0.0964	0.008	0.0941	0.0933	0.117	0.000847
Scale	–0.000299	–0.000223	0.00308	0.00192	0.000847	0.00271

TRTPAA, abiraterone acetate plus prednisolone treatment arm; ECOGENDDOXICAT0, ECOG=0 at docetaxel end; ECOGENDDOXICAT1, ECOG=1 at docetaxel end; ECOGENDDOXICAT2, ECOG=2 at docetaxel end.

Table 162: Time to third-line active treatment

	Intercept	**TRTPAA**	**NEWAGE**	**ECOGENDDOXICAT0**	**ECOGENDDOXICAT1**	**ANALGSBLCAT20**	**TTDISC2**	**Scale**
Intercept	0.477	–0.00958	–0.00569	–0.0622	–0.049	–0.018	–0.00014	–0.00157
TRTPAA	–0.00958	0.0242	–0.0000241	–0.00174	–0.00392	0.000695	0.0000216	–0.000416
NEWAGE	–0.00569	–0.0000241	0.0000842	0.00000644	–0.000193	0.0000815	0.000000545	0.000086
ECOGENDDOXICAT0	–0.0622	–0.00174	0.00000644	0.0825	0.0655	–0.00364	–0.0000147	–0.00304
ECOGENDDOXICAT1	–0.049	–0.00392	–0.000193	0.0655	0.0758	–0.000965	–0.0000112	–0.00188
ANALGSBLCAT20	–0.018	0.000695	0.0000815	–0.00364	–0.000965	0.0246	–0.00000681	0.000677
TTDISC2	–0.00014	0.0000216	0.000000545	–0.0000147	–0.0000112	–0.00000681	0.000000702	–0.00000605
Scale	–0.00157	–0.000416	0.000086	–0.00304	–0.00188	0.000677	–0.00000605	0.00383

TRTPAA, abiraterone acetate plus prednisolone treatment arm; NEWAGE, age at end of docetaxel treatment; ECOGENDDOXICAT0, ECOG=0 at docetaxel end; ECOGENDDOXICAT1, ECOG=1 at docetaxel end; ANALGSBLCAT20, baseline analgesic use level in last 24 hours; TTDISC2, days from docetaxel start to end.

Table 163: Time to death in BSC (before docetaxel) – AAP arm

	Intercept	**NEWAGEGRPNC_65**	**NEWAGEGRPNC65N7**	**ECOGDISC1CAT20**	**RAD_PROG_YN**	**LOG_PSABL**	**OPI_USE_YN**	**LOG_ALKPBL**	**Scale**
Intercept	0.749	0.0391	–0.00805	–0.00881	–0.0342	–0.0245	–0.0123	–0.119	0.0192
NEWAGEGRPNC_65	0.0391	0.273	0.0321	–0.0113	–0.00485	0.000399	–0.0166	–0.0087	0.0127
NEWAGEGRPNC65N7	–0.00805	0.0321	0.0683	–0.00723	–0.00796	0.0025	–0.0059	–0.00219	0.00505
ECOGDISC1CAT20	–0.00881	–0.0113	–0.00723	0.081	–0.0134	–0.00041	0.0161	0.000648	0.00546
RAD_PROG_YN	–0.0342	–0.00485	–0.00796	–0.0134	0.0589	0.00114	–0.00511	–0.00143	–0.00369
LOG_PSABL	–0.0245	0.000399	0.0025	–0.00041	0.00114	0.00686	–0.0000233	–0.00187	–0.00147
OPI_USE_YN	–0.0123	–0.0166	–0.0059	0.0161	–0.00511	–0.0000233	0.0568	–0.00107	–0.00074
LOG_ALKPBL	–0.119	–0.0087	–0.00219	0.000648	–0.00143	–0.00187	–0.00107	0.0262	–0.0015
Scale	0.0192	0.0127	0.00505	0.00546	–0.00369	–0.00147	–0.00074	–0.0015	0.00711

NEWAGEGRPNC_65, age <65 years at abiraterone acetate plus prednisolone (AAP) end; NEWAGEGRPNC65N7, age 65–75 years at AAP end; ECOGDISC1CAT20, ECOG=0 at AAP end; RAD_PROG_YN, radiographic progression at AAP end; LOG_PSABL, log baseline serum prostate specific antigen (ng/mL); OPI_USE_YN, opiate use at AAP end; LOG_ALKPBL, log baseline alkaline phosphatase (IU/L).

Table 164: Time to death in BSC (before docetaxel) – BSC (PP) arm

	Intercept	**newagecat240N60**	**newagecat260N70**	**newagecat270N80**	**newagecat280N85**	**ECOGDISC1CAT0**	**ECOGDISC1CAT1**	**ECOGDISC1CAT2**	**LOG_PSABL**	**OPI_USE_YN**	**LOG_LDHBL**	**Scale**
Intercept	5.35	–0.0136	–0.0165	–0.0873	0.0231	–0.16	–0.124	–0.258	–0.00284	–0.00612	–0.965	0.0267
newagecat240N60	–0.0136	0.867	0.109	0.0943	0.0761	–0.00539	0.0328	0.0223	0.000973	–0.0285	–0.0129	0.0175
newagecat260N70	–0.0165	0.109	0.151	0.0858	0.0708	–0.00743	0.0284	0.0201	0.00331	–0.0249	–0.0138	0.00992
newagecat270N80	–0.0873	0.0943	0.0858	0.114	0.07	0.0172	0.043	0.0329	0.00546	–0.0285	–0.00517	0.00625
newagecat280N85	0.0231	0.0761	0.0708	0.07	0.114	0.014	0.0331	0.0104	–0.000277	–0.0164	–0.019	0.00384
ECOGDISC1CAT0	–0.16	–0.00539	–0.00743	0.0172	0.014	0.189	0.138	0.136	0.00476	0.00672	–0.000577	0.00749
ECOGDISC	–0.124	0.0328	0.0284	0.043	0.0331	0.138	0.165	0.138	0.00518	–0.0115	–0.011	0.00495

1CAT1												
ECOGDISC 1CAT2	–0.258	0.0223	0.0201	0.0329	0.0104	0.136	0.138	0.214	0.00714	–0.00768	0.0146	0.00307
LOG_PSA BL	–0.00284	0.000973	0.00331	0.00546	–0.000277	0.00476	0.00518	0.00714	0.00646	–0.0013	–0.0061	–0.000622
OPI_USE_ YN	–0.00612	–0.0285	–0.0249	–0.0285	–0.0164	0.00672	–0.0115	–0.00768	–0.0013	0.0594	0.00313	–0.00123
LOG_LDH BL	–0.965	–0.0129	–0.0138	–0.00517	–0.019	–0.000577	–0.011	0.0146	–0.0061	0.00313	0.188	–0.0053
Scale	0.0267	0.0175	0.00992	0.00625	0.00384	0.00749	0.00495	0.00307	–0.000622	–0.00123	–0.0053	0.00624

newagecat240N60, age 40–59 years at best supportive care – placebo plus prednisolone (BSC [PP]) end ; newagecat260N70, age 60–69 years at BSC (PP) end; newagecat270N80, age 70–79 years at BSC (PP) end; newagecat280N85, age 80–84 years at BSC (PP) end; ECOGDISC1CAT0, ECOG=0 at BSC (PP) end; ECOGDISC1CAT1, ECOG=1 at BSC (PP) end; ECOGDISC1CAT2, ECOG=2 at BSC (PP) end; LOG_PSABL, log baseline serum prostate specific antigen (ng/mL); OPI_USE_YN, opiate use at BSC (PP) end; LOG_LDHBL, log value of lactate dehydrogenase at baseline.

Table 165: ECOG at discontinuation of AAP/BSC (PP)

Parameter	Intercept_0	Intercept_1	Intercept_2	TTDISC1	BMI	AGE	LOG_ALKPBL	BLECOGCAT0	BLECOGCAT1P
Intercept_0	1.08	1.1	1.1	–0.00004	–0.00979	–0.00655	–0.06	–0.0431	–
Intercept_1	1.1	1.13	1.13	–0.00005	–0.0099	–0.00675	–0.0615	–0.036	–
Intercept_2	1.1	1.13	1.18	–0.00005	–0.00992	–0.00681	–0.062	–0.0343	–
TTDISC1	–0.00004	–0.00005	–0.00005	0.000000102	–0.000000315	–1.05E–08	0.00000525	–0.00000632	–
BMI	–0.00979	–0.0099	–0.00992	–0.000000315	0.000242	0.000033	0.000092	0.000182	–
AGE	–0.00655	–0.00675	–0.00681	–1.05E–08	0.000033	0.000073	0.000055	0.000229	–
LOG_ALKPBL	–0.06	–0.0615	–0.062	0.00000525	0.000092	0.000055	0.011	0.000316	–
BLECOGCAT0	–0.0431	–0.036	–0.0343	–0.00000632	0.000182	0.000229	0.000316	0.0282	–
BLECOGCAT1P	–	–	–	–	–	–	–	–	–

TTDISC1, time from abiraterone acetetate plus prednisolone/best supportive care – placebo plus prednisolone (AAP/BSC [PP]) start to end; BMI, baseline body mass index; AGE, baseline age (years); LOG_ALKPBL, log baseline alkaline phosphatase (IU/L); BLECOGCAT0, ECOG=0 at baseline; BLECOGCAT1P, ECOG≥1 at baseline.

Table 166: ECOG at start of docetaxel

Parameter	Intercept_0	Intercept_1	TTDOX	AgeDOXST	BMI	ECOGDISC1CAT20	ECOGDISC1CAT21
Intercept_0	1.4	1.38	0.00006	–0.011	–0.016	–0.189	–0.144
Intercept_1	1.38	1.42	0.000027	–0.0111	–0.0167	–0.142	–0.119
TTDOX	0.00006	0.000027	0.000000733	–0.000000557	–0.000000486	–0.00009	–0.00005
AgeDOXST	–0.011	–0.0111	–0.000000557	0.000135	0.000051	0.000341	0.00002
BMI	–0.016	–0.0167	–0.000000486	0.000051	0.000459	–0.00071	–0.00077

ECOGDISC1CAT20	–0.189	–0.142	–0.00009	0.000341	–0.00071	0.212	0.17
ECOGDISC1CAT21	–0.144	–0.119	–0.00005	0.00002	–0.00077	0.17	0.179

TTDOX, time from abiraterone acetetate plus prednisolone/best supportive care – placebo plus prednisolone (AAP/BSC [PP]) end to docetaxel start; AgeDOXST, age at docetaxel start; BMI, baseline body mass index; ECOGDISC1CAT20, ECOG=0 at AAP/BSC (PP) end; ECOGDISC1CAT21, ECOG=1 at AAP/BSC (PP) end.

Table 167: ECOG at end of docetaxel

Parameter	Intercept_0	Intercept_1	Intercept_2	TTDISC1CAT30N183	TTDISC1CAT3184N548	TTDISC1CAT3549N731	LOG_PSABL	ECOGSTDOXCAT0	ECOGSTDOXCAT1
Intercept_0	0.832	0.792	0.782	–0.673	–0.682	–0.685	–0.015	–0.105	–0.0814
Intercept_1	0.792	0.804	0.793	–0.679	–0.683	–0.683	–0.0165	–0.0574	–0.064
Intercept_2	0.782	0.793	0.835	–0.681	–0.682	–0.682	–0.017	–0.0452	–0.0526
TTDISC1CAT30N183	–0.673	–0.679	–0.681	0.701	0.678	0.678	–0.00242	0.00547	0.0094
TTDISC1CAT3184N548	–0.682	–0.683	–0.682	0.678	0.696	0.678	–0.00111	0.0105	0.00982
TTDISC1CAT3549N731	–0.685	–0.683	–0.682	0.678	0.678	0.862	–0.00136	0.0146	0.0133
LOG_PSABL	–0.015	–0.0165	–0.017	–0.00242	–0.00111	–0.00136	0.00474	–0.00211	–0.00102
ECOGSTDOXCAT0	–0.105	–0.0574	–0.0452	0.00547	0.0105	0.0146	–0.00211	0.129	0.0754
ECOGSTDOXCAT1	–0.0814	–0.064	–0.0526	0.0094	0.00982	0.0133	–0.00102	0.0754	0.0845

TTDISC1CAT30N183, days from abiraterone acetetate plus prednisolone/best supportive care – placebo plus prednisolone (AAP/BSC [PP]) start to end <184; TTDISC1CAT3184N548, days from AAP/BSC (PP) start to end 184–548; TTDISC1CAT3549N731, days from AAP/BSC (PP) start to end 549–731; LOG_PSABL, log baseline serum prostate-specific antigen (ng/mL); ECOGSTDOXCAT0, ECOG=0 at docetaxel start; ECOGSTDOXCAT1, ECOG=1 at docetaxel start.

Table 168: ECOG at start of third-line treatment

Parameter	Intercept_0	Intercept_1	TTTRT3	LOG_PSABL	BLBPICAT0N1	ECOGENDDOXICAT20	ECOGENDDOXICAT21
Intercept_0	0.793	0.662	–0.00042	–0.04	–0.0883	–0.539	–0.49
Intercept_1	0.662	0.715	–0.00051	–0.0537	–0.0592	–0.372	–0.392
TTTRT3	–0.00042	–0.00051	0.0000027	0.000017	–0.00006	0.000104	0.000143
LOG_PSABL	–0.04	–0.0537	0.000017	0.014	–0.00552	–0.00912	–0.00511
BLBPICAT0N1	–0.0883	–0.0592	–0.00006	–0.00552	0.133	0.0256	0.0195
ECOGENDDOXICAT20	–0.539	–0.372	0.000104	–0.00912	0.0256	0.607	0.477
ECOGENDDOXICAT21	–0.49	–0.392	0.000143	–0.00511	0.0195	0.477	0.499

TTTRT3, days from docetaxel end to post-docetaxel treatment start; LOG_PSABL, log baseline serum prostate-specific antigen (ng/mL); BLBPICAT0N1, baseline Brief Pain Inventory 0–1; ECOGENDDOXICAT20, ECOG=0 at docetaxel end; ECOGENDDOXICAT21, ECOG=1 at docetaxel end.

Table 169: PSA progression at discontinuation of AAP/BSC (PP)

Parameter	Intercept	TRTPAA	TTDISC1	AGE
Intercept	0.428	–0.00165	–0.00005	–0.00575
TRTPAA	–0.00165	0.029	–0.00003	–0.00008
TTDISC1	–0.00005	–0.00003	0.000000312	–4.89E–08
AGE	–0.00575	–0.00008	–4.89E–08	0.000082

TRTPAA, abiraterone acetetate plus prednisolone (AAP) treatment arm; TTDISC1,tTime from AAP/best supportive care – placebo plus prednisolone (BSC [PP]) start to end; AGE, baseline age.

Table 170: Radiographic progression at discontinuation of AAP/BSC (PP)

Parameter	Intercept	TRTPAA	TTDISC1	age_less_65	PSA_PROG_YN	BNMETNo
Intercept	0.0398	–0.00776	–0.00003	–0.00869	–0.0173	–0.0138
TRTPAA	–0.00776	0.0239	–0.00001	0.000335	0.00163	–0.00135
TTDISC1	–0.00003	–0.00001	0.000000149	0.00000585	–0.00002	0.00000492
age_less_65	–0.00869	0.000335	0.00000585	0.0308	–0.00093	–0.00023
PSA_PROG_YN	–0.0173	0.00163	–0.00002	–0.00093	0.0307	0.0019
BNMETNo	–0.0138	–0.00135	0.00000492	–0.00023	0.0019	0.0229

TRTPAA, abiraterone acetetate plus prednisolone (AAP) treatment arm; TTDISC1, time from AAP/best supportive care – placebo plus prednisolone (BSC [PP]) start to end; age_less_65, baseline age <65 years; PSA_PROG_YN, prostate-specific antigen progression at AAP/BSC (PP) end; BNMETNo, no bone metastasis at baseline.

Table 171: Opiate use at discontinuation of AAP/BSC (PP)

Parameter	Intercept	BMI	DIAG2RAN	LOG_ALKPBL	ANALGSBLCAT0	ANALGSBLCAT1	BLBPICAT0N1
Intercept	1.06	–0.0113	–0.00001	–0.0847	–0.279	–0.28	–0.0211
BMI	–0.0113	0.000336	5.16E–08	0.000215	0.000497	0.000407	–0.0002
DIAG2RAN	–0.00001	5.16E–08	2.75E–09	0.00000069	0.00000362	0.00000406	0.00000026
LOG_ALKPBL	–0.0847	0.000215	0.00000069	0.0157	0.000118	–0.0003	0.00311
ANALGSBLCAT0	–0.279	0.000497	0.00000362	0.000118	0.28	0.263	–0.0164
ANALGSBLCAT1	–0.28	0.000407	0.00000406	–0.0003	0.263	0.284	–0.00293
BLBPICAT0N1	–0.0211	–0.0002	0.00000026	0.00311	–0.0164	–0.00293	0.037

AAP, abiraterone acetetate plus prednisolone; BSC, best supportive care; CST, corticosteroids; BMI, baseline body mass index; DIAG2RAN, days from diagnosis to randomisation; LOG_ALKPBL, log baseline alkaline phosphatase (IU/L); ANALGSBLCAT0, baseline analgesic use level in last 24 hours of 0; ANALGSBLCAT1, baseline analgesic use level in last 24 hours of 1; BLBPICAT0N1, baseline BPI #3 0–1.

Table 172: Time to third-line active treatment discontinuation

	Intercept	TRTPAA	Scale
Intercept	0.0128	–0.0128	0.000705
TRTPAA	–0.0128	0.029	–0.00083
Scale	0.000705	–0.00083	0.00475

TRTPAA, abiraterone acetate plus prednisolone treatment arm.

Table 173: Post-docetaxel treatment end to death

	Intercept	TRTPAA	NewAgePostDocEnd	DIAGYRSPostDocTxEnd0-3	Scale
Intercept	0.722	–0.0181	–0.0101	–0.111	0.00321
TRTPAA	–0.0181	0.0387	0.0000397	–0.00721	0.000257
NewAgePostDocEnd	–0.0101	0.0000397	0.000145	0.00147	–0.0000276
DIAGYRSPostDocTxEnd0-3	–0.111	–0.00721	0.00147	0.0753	–0.00156
Scale	0.00321	0.000257	–0.0000276	–0.00156	0.00592

TRTPAA, abiraterone acetate plus prednisolone treatment arm; NewAgePostDocEnd, age at post-docetaxel treatment end; DIAGYRSPostDocTxEnd0-3, years to diagnosis <3.

10.17 Appendix 17: Supplementary utility study methods and results

Methods

Study methods, measures and other materials were designed to follow methodological requirements for HTA bodies including NICE [167]. Validated measures used in this study offer two methods for calculating utility data, including the preferred method for meeting the NICE reference case (EQ-5D). Validated cancer and prostate cancer-specific HRQL measures were included to capture additional detail of HRQL impact of mCRPC for evaluation of variation in impact across the course of treatment and disease progression.

The screening and background/medical history questions were developed with clinical input. The online screening, consent and survey materials were piloted with four eligible patients (who between them covered the first, second and fourth stratified treatment phases to ensure suitability of the materials before main data collection).

All study materials were reviewed and approved by an independent review board (RCRC Independent Review Board, LLC, www.rcrcirb.com; Protocol 2604-0020; initial approval date 16 May 2013) as well as Janssen drug safety and patient information review boards (PRP, ZINC).

Participant screening and recruitment

Eligible participants were recruited through a specialist patient recruitment agency and via the Prostate Cancer Support Federation through their existing support groups. To further support study recruitment, study information was posted on relevant areas of the Cancer Research UK website. Participants' eligibility for enrolment in the study was assessed by screening items, which were completed online by potential participants. Inclusion and exclusion criteria are shown in Table 174.

Table 174: Inclusion and exclusion criteria for participants in the utility study

Inclusion criteria	Exclusion criteria	Additional exclusion criteria for asymptomatic/mildly symptomatic participants (subgroup 1)
• [redacted]	[redacted]	• [redacted]

BPI, brief pain inventory; mCRPC, metastatic castration-resistant prostate cancer.

Procedures

Potential participants were provided with an electronic link (Uniform Resource Locator)) for access to the study survey website. Potential participants first

completed the screening items to assess eligibility and categorise them into relevant treatment phases. Duplicate completion of the survey by a single participant was prevented by an identity check based on IP address, UK post-code, age, and treatment phase.

Eligible participants then completed an online informed consent procedure where information about the study was presented (e.g. study purpose, types of questions included in the survey, data access) before being asked to indicate that they understood the nature of the study and their rights, and that they agreed to participate in the study.

Following consent, participants completed the online survey comprising basic background and medical history information, and validated questionnaires designed to collect current health utility (EQ-5D) and cancer-specific HRQL data (EORTC QLQ-C30 and PR25).

[redacted]

Measures
Following informed consent, participants were asked to complete the online survey comprising:

1. Screening form, to identify eligible patients and categorise participants into one of the four treatment phases
2. Background and medical history information, to collect basic demographic and clinical data
3. EQ-5D-5L, a six-item questionnaire that has been designed and validated by the EuroQol group for collecting health utilities [256]. The EQ-5D-5L classifies health states across five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a VAS
4. EORTC QLQ C-30, a 30-item questionnaire developed to assess QoL in cancer patients [257]
5. EORTC QLQ PR-25, which contains 25 QoL questions specific for prostate cancer patients [258]. As for the QLQ-C30, a higher score on the functional sub-scales indicates a higher/healthier level of functioning, whereas higher symptom scores indicates a higher level of symptomatology/problems.

Data analysis
EORTC QLQ C-30 and PR-25 data were scored according to validated scoring instructions [259;260]. The EQ-5D-5L values were converted into a summary utility index by applying scores from a standard set of UK societal preference weights [169]. Background and medical history data were summarised by descriptive statistics (means, SDs and proportions, as appropriate) to describe sample and subgroup characteristics. EQ-5D-5L, EORTC QLQ C-30 and PR-25 data were summarised by means and SDs according to the treatment phases outlined in above sections. Summary descriptive statistics of EQ-5D-5L and EORTC QLQ-C-30 preference-weighted utilities for the first subgroup were further broken down by age group (<65, 65–75, >75 years), BPI #3 (0–1, 2–3), ECOG PS (0, 1), and presence of progressive disease (as per PSA level and/or scan) to provide additional utility

values for asymptomatic or mildly symptomatic mCRPC patients after failure of ADT, before receiving chemotherapy.

Results

The pattern of impact reflected by the EORTC QLQ-C30 global health status is similar to that shown by the utility data, with [redacted] (asymptomatic/mildly symptomatic before receiving chemotherapy), lowest scores from the second treatment phase (symptomatic before receiving chemotherapy) (Table 175). Global health status of men in the third and fourth treatment phases (currently receiving chemotherapy and post-chemotherapy) [redacted].

Table 175: EORTC QLQ C-30 domain scores by treatment phase

	mCRPC treatment phase			
	Asymptomatic/ mildly symptomatic post-ADT, pre-chemotherapy (N=50)	**Symptomatic post-ADT pre-chemotherapy (N=50)**	**Currently receiving chemotherapy (N=17)**	**Post-chemo-therapy (N=46)**
Global health status/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Functional scales				
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scales/items				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Nausea and vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]

Data are mean (SD).
QoL, quality of life; SD, standard deviation.

Compared with men in the second, third, and fourth mCRPC treatment phases, asymptomatic/mildly symptomatic pre-chemotherapy (first mCRPC treatment phase) reported [redacted]. They also reported [redacted]. [redacted] were particular areas of HRQL for symptomatic patients who had not received chemotherapy (second mCRPC treatment phase). [redacted] was also particularly impacted for those receiving chemotherapy (third mCRPC treatment phase). In

terms of symptoms, scores were [redacted] amongst the first treatment phase participants across the range captured by the EORTC QLQ-C30 compared with the second, third and fourth treatment phases. Patients in the second treatment phase scored highest for [redacted]. Patients in the third treatment phase scored highest for [redacted].

In terms of prostate cancer-specific HRQL, wide SDs and small sample sizes make it hard to draw conclusions about any differences between respective treatment phases in terms of sexual activity and sexual functioning (Table 176). However, asymptomatic/mildly symptomatic pre-chemotherapy patients (first mCRPC treatment phase) reported [redacted] than those in the other mCRPC treatment phases and [redacted] than symptomatic pre-chemotherapy patients and those receiving chemotherapy (second and third mCRPC subgroups). Mean scores for [redacted] were lower in chemotherapy naïve patients (first and second subgroups) than those receiving/post-chemotherapy (third and fourth subgroups), although wide SDs around the mean values for the first and second mCRPC treatment phases indicate considerable variation in experience.

Table 176: EORTC QLQ PR-25 domain scores by treatment phase

	mCRPC treatment phase			
	Asymptomatic/ mildly symptomatic post-ADT, pre-chemotherapy (N=50)	**Symptomatic post-ADT, pre-chemotherapy (N=50)**	**Currently receiving chemotherapy (N=17)**	**Post-chemo-therapy (N=46)**
Functional scales[a]				
Sexual activity	[redacted]	[redacted]	[redacted]	[redacted]
Sexual functioning[b]	[redacted]	[redacted]	[redacted]	[redacted]
Symptom scales[c]				
Urinary symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Bowel symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Hormonal treatment-related symptoms	[redacted]	[redacted]	[redacted]	[redacted]
Incontinence aid	[redacted]	[redacted]	[redacted]	[redacted]

[a]A score of 100 indicates the best score.
[b]Scores from 28 men (5, 9, 7, 7 in the four groups, respectively).
[c]A score of 100 indicates the worst score.

10.18 Appendix 18: Mapping study

Objectives

The goal of this analysis was to estimate utility values to inform the economic model based on the COU-AA 302 and COU-AA-301 trials of AAP versus PP for the treatment of mCRPC. Utilities estimated from the trial would assure that the values applied to the model reflect the patient population eligible for AAP. This would also permit potential utility differences from treatment differences between AAP and PP to be quantified.

Methods

Converting FACT-P to EQ-5D utility score

HRQL of patients in the trial was measured using FACT-P questions. This scale comprises the 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. The prostate cancer subscale of the FACT-P includes 12 items specifically designed to measure the HRQL in prostate cancer patients. While the FACT-P offers a well-validated and clinically meaningful assessment of disease burden, it does not offer a preference-adjusted health status (utility) value between 0 (dead) and 1 (full health) that are essential to pharmacoeconomic models. The EQ-5D assessment is a standardised and validated generic instrument that establishes these preference-adjusted utility values. However, because the EQ-5D assessment was not administered in the AA Phase III trials, utility scores had to be derived based on an algorithm for mapping FACT-P scores to EQ-5D scores described by Diels et al. 2012 [155].

Diels et al. [155] was an observational study collecting HRQL data from [redacted] mCRPC patients in Belgium, France, Germany, Sweden, the Netherlands, and the UK. In this analysis, utility values were derived from EQ-5D profiles, while the predictive validity of the five FACT-P subscales was tested using OLS, median, Gamma and Tobit multivariate regression models. The results of this study found that OLS was the best performing model, and all FACT-P subscales were significantly predictive.

Table 177: Comparison coefficients OLS model [155]

	Estimate	Standard error	p value
Intercept	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Age^2	[redacted]	[redacted]	[redacted]
PWB	[redacted]	[redacted]	[redacted]
SWB	[redacted]	[redacted]	[redacted]
EWB	[redacted]	[redacted]	[redacted]
EWB^2	[redacted]	[redacted]	[redacted]
FWB	[redacted]	[redacted]	[redacted]
FWB^2	[redacted]	[redacted]	[redacted]
PCS	[redacted]	[redacted]	[redacted]

OLS, ordinary least squares.

Identifying predictors that impact EQ-5D utility score

As the aim of this analysis was to derive an equation to be used in the economic analysis, only predictors that were relevant for the economic model were considered. For the model, the starting utility and utility impact while patients were on treatment and free of disease progression was needed to compare AAP versus PP for the ITT. To use the trial-based utilities to inform the chemotherapy comparators, it was also necessary to quantify the impact of grade 3/4 AEs, since different comparators differ in their safety profile.

Predictors tested

- Treatment
- AEs of grade 3 or higher

First, an analytical dataset was created that included one record per patient per visit with non-missing change from baseline in utility score. Time-dependent indicators of progression were derived such that for all visits prior to progression the indicators were set to 0 and changed to 1 once patient progressed. Time-dependent indicators of AEs were derived such that they were set to 0 prior to first onset of the AE and to 1 for all visits after that.

Only the multivariate regression prediction models used in the model are described here:

- Impact of AEs on utility: A model that included only baseline utility and any Grade 3/4 AE was also developed. A repeated measures mixed-effect model was used to predict the change from baseline in utility score over time. The rationale for this model is that grade 3/4 AEs are the reliably and homogeneously reported outcomes for comparators in the literature and as such are included in the economic model as differentiators. This regression model allows for the effect of Grade 3/4 AEs on baseline utility to be assessed. This utility effect can then be applied to the Grade 3/4 AE profile of the various comparators in the economic model and thus differentiate their patient utilities resulting from the use of each treatment.
- Impact of treatment: A model was created that only included baseline utility and treatment. This model directly estimates the utility effect of being on treatment (i.e. AAP). This model does not include mediating variables like AEs because these variables may attenuate the effect of treatment. When mediating variables are excluded from the model, the direct effect of being on treatment on utility can be ascertained.

Results

Distributions of the baseline utility score in each treatment arm for the ITT population are summarised in Table 178. Also presented are the mean utility values for the UK patients in the trial, but these were not used in the economic model. Overall mean±SD utility scores were similar in the AAP and PP arms ([redacted] and [redacted], respectively) with the middle two quartiles of patients scoring [redacted]–[redacted].

Table 178: Mean utility value and baseline COU-AA-302 – by analysis groups and treatment arm (ITT population)

Treatment group	Country	N obs	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
AAP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AA, abiraterone acetate plus prednisolone; ITT, intention-to-treat; PP, placebo plus prednisolone; SD, standard deviation.

Table 179 summarises utility scores at the end of treatment visit for the ITT population. Overall utility score at the end of treatment visit was higher in placebo group compared to treatment group; [redacted] and [redacted], respectively. Results of this analysis were not used in the model, given the relatively small number of patients left to inform this mean. Table 180 and Table 181 summarise the baseline and end of treatment utility of the COU-AA-301 population.

Table 179: Mean utility value at end of treatment COU-AA-302 – by analysis groups and treatment arm (ITT population)

Treatment group	Country	N obs	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
AAP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AA, abiraterone acetate plus prednisolone; ITT, intention-to-treat; PP, placebo plus prednisolone; SD, standard deviation.

Table 180: Mean utility value baseline COU-AA-301 – by analysis groups and treatment arm (ITT population)

Treatment group	Country	N obs	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
AAP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AA, abiraterone acetate plus prednisolone; ITT, intention-to-treat; PP, placebo plus prednisolone; SD, standard deviation.

Table 181: Mean utility value end of treatment COU-AA-301 – by analysis groups and treatment arm (ITT population)

Treatment group	Country	N obs	N	Mean	SD	Min	Lower quartile	Median	Upper quartile	Max
AAP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AA, abiraterone acetate plus prednisolone; ITT, intention-to-treat; PP, placebo plus prednisolone.

Results of the multiple regression analyses used to inform the model are summarised in Table 182. Experiencing any grade ≥3 AE had a utility impact of –0.06487 during the time on treatment. AAP patients had a mean 0.02126 point higher utility score than PP patients, and the effect was statistically significant.

Table 182: Results of multiple regression analyses: change from baseline in utility score over time (all patients)

Predictors	Baseline utility, any AE, pain progression, and PSA response		Baseline utility and treatment	
	Estimate	p value	Estimate	p value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment group: AAP vs. PP			[redacted]	[redacted]
Baseline utility score	[redacted]	[redacted]	[redacted]	[redacted]
Any grade 3/4 AE	[redacted]	[redacted]		

AA, abiraterone acetate plus prednisolone; ITT, intention-to-treat; PP, placebo plus prednisolone; PSA, prostate-specific antigen; SD, standard deviation.

10.19 Appendix 19: MRU related to AE analysis

MRU associated with the occurrence of clinical events was collected in the COU-AA-302 and COU-AA-301 trials. This MRU data specifically captured unscheduled resource use driven by clinical events; MRU related to regularly scheduled disease follow-up was neither collected in the trial nor included in this analysis. In an effort to characterise and calculate the cost of this unscheduled MRU for use in the economic model of AAP versus BSC (PP), we conducted a two-phase statistical analysis on these data. In Phase I, we explored the timing of the resource use by treatment arm, using data from all patients in all study countries, to identify how best to apply MRU costs in the economic model. In Phase II, we quantified the incurred MRU costs specific to the UK by treatment arm. Both analyses are described in greater detail as follows:

Phase I analysis

The objective of the Phase I analysis was to understand the MRU patterns by treatment group and evaluate their dependence on duration of treatment (considered a proxy for PFS in the economic model).

Analysis approach

As will be demonstrated by the results of the Phase II analysis below, our analysis of MRU patterns focused on hospitalisations and outpatient visits, as these were the potential drivers of total MRU costs. Hospitalisation and outpatient visit rates during the PFS/on treatment phase of the COU-AA-302 trial were estimated per patient as well as per 100 patient-weeks. Patients who were still on treatment at the end of trial were excluded from the analysis, as these individuals were not yet expected to have complete PFS records. In addition, we suspected that a certain percentage of patients with no MRU had indeed incurred MRU but not had the data collected. As such, we performed our analysis twice – once where we included patients with no MRU data, and once where we excluded them.

Results

For the COU-AA-302 trial, the rate of hospitalisation per 100 person-weeks was slightly lower for AAP than for PP when all patients in all study countries were considered (1.01 vs. 1.03 when patients without MRU records were included, and 1.58 vs. 1.68 when patients without MRU records were excluded) (Table 183). The rate of outpatient visit (including general practitioner, pharmacist, registered nurse, and social service visits) per 100 person-weeks were slightly higher for AAP than for PP when patient without MRU records were included (1.39 vs. 1.37), but were slightly lower for AAP when patients without MRU records were excluded (2.16 vs. 2.25) (Table 184).

For the COU-AA-301 trial, the rate of hospitalisation per 100 person-weeks was slightly lower for AAP than for PP when all patients in all study countries were considered (2.83 vs. 3.36 when patients without MRU records were included, and 4.04 vs. 5.28when patients without MRU records were excluded) (Table 183).

Despite the slight differences in rates of hospitalisation and outpatient visit per 100 person-weeks between treatment groups, the Phase I analysis of all patients in all study countries suggests that MRU during the entire period in which a patient is

progression free is similar between the two arms of the COU-AA-302 trial and the two arms of the COU-AA-301 trial, despite a statistically significant difference in PFS duration observed in the trials. The analysis shows that the hospitalisation and outpatient visit rates for all patients per PFS stage per treatment arm are not statistically significant across the two treatment groups.

Table 185 and Table 186 present these rates by treatment group, including and excluding patients with no MRU events. The implication of the results described above is that MRU in the progression-free health state is not statistically significantly different between the two arms of the COU-AA-302 trial and the two arms of the COU-AA-301 trial.

Table 183: Hospitalisation rate per 100 person-weeks

Country	Treatment Group	Rate per 100 Person-weeks (including patients w/o MRU record)				Rates per 100 Patient-weeks (including patients w/ MRU records only)			
		N	Hosp ICU	Hosp-non-ICU	Hosp-any	N	Hosp ICU	Hosp-non-ICU	Hosp-any
COU-AA-302 MRU									
All	AA	419	0.1	0.96	1.01	255	0.16	1.5	1.58
All	PP	482	0.13	0.96	1.03	253	0.21	1.57	1.68
Canada	AA	49	0	0.65	0.65	32	0	0.98	0.98
Canada	PP	29	0	0.42	0.42	15	0	0.72	0.72
UK	AA	32	0.11	0.9	0.9	15	0.22	1.72	1.72
UK	PP	49	0	0.78	0.78	26	0	1.37	1.37
US	AA	183	0.063	0.68	0.73	111	0.094	1.01	1.09
US	PP	221	0.12	0.69	0.77	128	0.18	1.02	1.14
COU-AA-301 MRU									
All	AA	672	0.526	2.393	2.826	457	0.752	3.422	4.040
All	PP	380	0.640	2.819	3.358	235	1.007	4.435	5.283
Canada	AA	79	0.292	1.605	1.751	66	0.341	1.873	2.044
Canada	PP	55	0.319	2.338	2.656	40	0.478	3.506	3.984
UK	AA	104	0.299	4.220	4.519	86	0.347	4.900	5.247
UK	PP	61	0.404	4.097	4.328	50	0.499	5.061	5.346
US	AA	284	0.475	1.776	2.176	166	0.799	2.987	3.661
US	PP	152	0.239	1.914	2.123	73	0.453	3.624	4.021

AAP, abiraterone acetate plus prednisolone; ICU, intensive care unit; MRU, medical resource utilisation.

Table 184: Outpatient visit rate per 100 person-weeks (COU-AA-302 MRU)

Country	Treatment group	Rate per 100 person-weeks (including patients w/o MRU record)		Rates per 100 patient-weeks (including patients w/ MRU records only)	
		N	Outpatient visits	N	Outpatient visits
All	AAP	419	1.39	255	2.16
All	PP	482	1.37	253	2.25
Canada	AAP	49	1.76	32	2.67
Canada	PP	29	1.76	15	3.00
UK	AAP	32	2.38	15	4.52
UK	PP	49	3.23	26	5.66
US	AAP	183	0.58	111	0.87
US	PP	221	1.16	128	1.73

AAP, abiraterone acetate plus prednisolone; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Table 185: Hospitalisation rate per treatment/progression-free phase

Country	Treatment group	Rate per treatment/progression-free phase (including patients w/o MRU record)				Rates per treatment/progression-free phase (including patients w/ MRU records only)			
		N	Hosp ICU	Hosp-non-ICU	Hosp-any	N	Hosp ICU	Hosp-non-ICU	Hosp-any
COU-AA-302 MRU									
All	AAP	419	0.0001	0.0014	0.0014	255	0.0002	0.0021	0.0023
All	PP	482	0.0002	0.0014	0.0015	253	0.0003	0.0022	0.0024
Canada	AAP	49	0	0.0009	0.0009	32	0	0.0014	0.0014
Canada	PP	29	0	0.0006	0.0006	15	0	0.001	0.001
UK	AAP	32	0.0002	0.0013	0.0013	15	0.0003	0.0025	0.0025
UK	PP	49	0	0.0011	0.0011	26	0	0.002	0.002
US	AAP	183	>0.000	0.001	0.001	111	0.0001	0.0014	0.0016
US	PP	221	0.0002	0.001	0.0011	128	0.0003	0.0015	0.0016
COU-AA-301 MRU									
All	AAP	672	0.159	0.725	0.856	457	0.234	1.066	1.258
All	PP	380	0.150	0.661	0.787	235	0.243	1.068	1.272
Canada	AAP	79	0.101	0.557	0.608	66	0.121	0.667	0.727
Canada	PP	55	0.055	0.400	0.455	40	0.075	0.550	0.625
UK	AAP	104	0.077	1.087	1.163	86	0.093	1.314	1.407
UK	PP	61	0.115	1.164	1.230	50	0.140	1.420	1.500
US	AAP	284	0.134	0.500	0.613	166	0.229	0.855	1.048
US	PP	152	0.053	0.421	0.467	73	0.110	0.877	0.973

AAP, abiraterone acetate plus prednisolone; ICU, intensive care unit; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Table 186: Outpatient visit rate per treatment/progression-free phase

Country	Treatment group	Rate per treatment/progression-free phase (including patients w/o MRU record)		Rates per treatment/progression-free phase (including patients w/ MRU records only)	
		N	Outpatient visit	N	Outpatient visit
COU-AA-302 MRU					
All	AAP	419	**0.0019**	255	**0.0031**
All	PP	482	**0.0019**	253	**0.0032**
Canada	AAP	49	**0.0025**	32	**0.0038**
Canada	PP	29	**0.0025**	15	**0.0043**
UK	AAP	32	**0.0033**	15	**0.0065**
UK	PP	49	**0.0046**	26	**0.0081**
US	AAP	183	**0.0007**	111	**0.0011**
US	PP	221	**0.0016**	128	**0.0026**

AAP, abiraterone acetate plus prednisolone; MRU, medical resource utilisation; PP, placebo plus prednisolone.

Phase II analysis

The objective of the Phase II analysis was to understand the costs associated with unscheduled or event driven resources consumed by the UK subgroup with the COU-AA-302 and COU-AA-301 trials.

Analysis approach for the UK subgroup

Resource use collected using the CRF from the COU-AA-302 trial were classified into five categories: 1) hospitalisations (note: length of stay data were not collected), 2) GP visits, 3) nurse visits, 4) site investigator visits (assumed to be urologist visits), and 5) other (free text such as emergency department, computed tomography scan).

Each resource use item was assigned a UK unit cost, based on standard sources (National Schedule of Reference Costs 2011-12; PSSRU 2011 [261]). The unit costs were aggregated at patient level to estimate a total per-patient cost.

Patient-level data were excluded for patients remaining on treatment at the end of trial from the cost analysis as they were not expected to have full information for the progression-free treatment phase.

Our analysis estimated the cost per person-week and total cost per patient during the entire treated period. Generalised linear models were used to estimate the impact of the treatment group and treatment duration on total cost per patient.

Results

Thirty-two AAP patients and 49 PP patients were included in the Phase II UK subgroup MRU analysis. Among these patients, 17 AAP patients and 23 PP patients had no resource utilisation record. Because the COU-AA-302 population included asymptomatic and mildly symptomatic mCRPC patients, it was assumed that these patients with no resource utilisation record incurred no resource use while they were progression free. The total cost per patient was higher in the AAP arm, but it was not statistically significantly different from the cost per patient in the PP arm (Table 187). The average cost per patient for AAP was £1410.11 compared to £647.29 for PP. The cost of outpatient visits was the major driver for the total MRU cost. Despite the differences in the average cost, when tested in the Gamma model, AA treatment was not associated with statistically significantly higher cost, with or without treatment duration included in the analysis (Table 188). On the contrary, treatment duration was associated with statistically significantly higher cost, with or without treatment arm included in the analysis (Table 188). Overall, the results indicated that the unplanned MRU cost was independent of treatment arm but dependent on the treatment duration. Therefore, in the model, a weekly unplanned MRU cost (£21.57 per week) was applied to both treatment arms for the duration patients stayed on treatment.

In a similar analysis for the UK subgroup of the COU-AA-301 trial, it was found that the unplanned event-drive MRU was neither dependent on treatment arm nor treatment duration. The patients incurred £2,800.44 MRU cost per PFS phase or £87.44 per week to be comparable to the COU-AA-301 MRU cost.

Table 187: Total MRU per patient (study COU-AA-302)

Treatment group	N	Cost per patient, £		Cost per person-week, £
		Mean	SD	
AAP	32	1410.11	3238.22	25.51
PP	49	647.29	1379.15	17.69
All	81			21.57

AAP, abiraterone acetate plus prednisolone; PP, placebo plus prednisolone; SD, standard deviation.

Table 188: Regression analysis to assess the impact of treatment and treatment duration on unplanned MRU cost

Analysis of maximum likelihood parameter estimates (treatment only)								
Parameter		DF	Estimate	Standard error	Wald 95% confidence limits		Wald Chi-square	Pr > ChiSq
Intercept		1	6.7779	0.2913	6.2069	7.3489	541.23	<0.0001

Treatment	AAP	1	0.6741	0.4450	–0.1981	1.5464	2.29	0.1298
Treatment	PP	0	0.0000	0.0000	0.0000	0.0000	–	–
Scale		1	0.2104	0.0231	0.1696	0.2609		
Analysis Of maximum likelihood parameter estimates (treatment and treatment duration)								
Parameter		**DF**	**Estimate**	**Standard error**	**Wald 95% confidence limits**		**Wald Chi-square**	**Pr > ChiSq**
Intercept		1	5.8163	0.3873	5.0573	6.5753	225.58	<0.0001
Treatment	AAP	1	0.4165	0.4452	-0.4561	1.2890	0.88	0.3496
Treatment	PP	0	0.0000	0.0000	0.0000	0.0000	–	–
Treatment Duration_WEEKS		1	0.0154	0.0054	0.0049	0.0258	8.24	0.0041
Scale		1	0.2212	0.0244	0.1782	0.2745		
Analysis of maximum likelihood parameter estimates (treatment duration only)								
Parameter		**DF**	**Estimate**	**Standard error**	**Wald 95% confidence limits**		**Wald Chi-square**	**Pr > ChiSq**
Intercept		1	5.9504	0.3696	5.2261	6.6748	259.23	<0.0001
Treatment Duration_WEEKS		1	0.0165	0.0053	0.0062	0.0268	9.83	0.0017
Scale		1	0.2200	0.0242	0.1772	0.2730		

AAP, abiraterone acetate plus prednisolone; PP, placebo plus prednisolone.

10.20 Appendix 20: Univariate and Probabilistic Sensitivity Analysis for the base case without the PAS

The results of the one-way sensitivity analysis, for the base case without the PAS applied, are summarised in Table 189, showing the lower and upper ICER limits generated by the simulation model using the public price in the UK. Model settings were consistently set using a sampling method of 10 trial replications to ensure the most stable results. The accompanying tornado diagram is shown in Figure 43. The majority of cases within the deterministic sensitivity analyses indicated that the results were relatively stable across a range of assumptions. The model was most sensitive to post-ADT baseline utility, discounting, 1st-line treatment duration and a shorter time horizon.

Table 189: Results of univariate sensitivity analysis without PAS

	Base-case parameter	**Proposed variation**	**ICER, £/QALY**
Model ICER without PAS			[redacted]
Model settings			
Time horizon	Life time	10 years	[redacted]
Discount rate: health effects	3.5% for health effects & costs	0–5% for health effects 3.5% for costs	[redacted]
Discount rate: costs	3.5% for health effects & costs	3.5% for health effects 0–5% for costs	[redacted]
Discount rate: for health effects & costs	3.5% for health effects & costs	0–5% for health effects & costs	[redacted]
Clinical settings			
Truncation of OS curve at 1%	Truncated	Non-truncated	[redacted]
Distribution for 1st-line treatment duration	Log-logistic (best fit)	Weibull only	[redacted]
		2-segment curve	[redacted]
Cost inputs			
AA 1st-line compliance	98%	95–100%	[redacted]
Scheduled MRU	As per MRU study	25th–75th percentile on all scheduled MRU	[redacted]
Unplanned MRU	As per COU-AA-302 trial	±20% on all unplanned MRU costs	[redacted]
Utility inputs			
Post-ADT baseline	[redacted]	±20% [redacted]	[redacted]
Docetaxel	[redacted]	±20% [redacted]	[redacted]
BSC/APP post-docetaxel; BSC (before death)	[redacted]; 0.500	±20% [redacted]; 0.4–0.6)	[redacted]

[redacted]43[redacted]
PSA for the base case without the PAS is presented in Figure 44.

[redacted]

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being

undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes ‘commercial in confidence’ information and data that are awaiting publication (‘academic in confidence’). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the manufacturer’s or sponsor’s responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and information submitted under ‘academic in confidence’ in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its

guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.