Abiraterone acetate for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy

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Contents

List of Tables and Figures

Tables

Figures

Abbreviations

AAP	Abiraterone acetate plus prednisolone
ADT	Androgen-Deprivation Therapy
AE	Adverse Event
AIC	Akaike Information Criterion
AS	Analgesic Score
ASCO	American Society of Clinical Oncology
BFI-SF	Brief Fatigue Inventory – Short Form
BIC	Bayesian Information Criterion
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CI	Confidence interval
CIC	Commercial In Confidence
CRPC	Castration-Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Circulating Tumour Cell
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DSU	Decision Support Unit
EAU	European Association of Urology
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
EoL	End of Life
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FDA	Food and Drug Administration
GLM	Generalized Linear Model
GNRH	Gonadotropin-Releasing Hormone
GCSF	Granulocyte-Colony Stimulating Factors
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IQR	Interquartile Range
ITT	Intention To Treat
IV	Intravenous
KM	Kaplan-Meier
LHRH	Luteinising Hormone-Releasing Hormone
mCRPC	Metastatic Castration-Resistant Prostate Cancer
M	Mitoxantrone
MITOX	Mitoxantrone
MP	Mitoxantrone plus Prednisolone
mPFS	Modified Progression-Free Survival
MRI	Magnetic Resonance Imaging
MRU	Medical Resource Use
MS	Manufacturer's Submission
OP	Out Patient
OPC	One Prior Chemotherapy
OS	Overall Survival
PAS	Patient Access Scheme
PC	Prostate Cancer
PFS	Progression-Free Survival
PP	Placebo plus prednisolone
PPI	Present Pain Intensity
PR	Partial Response

PRESS	Peer Review of Electronic Search Strategies
PRO	Patient Reported Outcome
PSA	Prostate-Specific Antigen
PSAWG	Protocol Specific Antigen Working Group
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit.
P-Y	Patient-Years
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
rPFS	Radiological Progression-Free Survival
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SRE	Skeletal-Related Event
STA	Single Technology Assessment
TAG	Technology Assessment Guideline
TTO	Time Trade Off
UCI	Upper Confidence Interval
VAS	Visual Analogue Scale

1. SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer's scope encompasses the clinical and cost effectiveness of abiraterone used together with prednisolone within its licensed indication for second line treatment of metastatic castration-resistant prostate cancer (mCRPC) which has progressed during or after docetaxel therapy. Comparisons are made with best supportive care (BSC, to include prednisolone) or mitoxantrone with or without prednisolone. There were a few differences between the NICE and manufacturer's scopes and these are summarised below.

The European marketing authorisation recommended abiraterone in combination with prednisone or prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel based chemotherapy.

The indicated population was further refined in the manufacturer's scope as a "One prior chemotherapy" (OPC) population, defined as patients who have received only docetaxel chemotherapy prior to abiraterone. The manufacturer considered this necessary, partly because the clinical evidence in the MS came from a trial in which some patients had already received more than one type of chemotherapy (i.e. docetaxel and one other) before receiving abiraterone, and also because the manufacturer considered that this OPC population would more closely reflect the mCRPC patients in England and Wales who would receive abiraterone therapy; i.e. it would be unlikely that after docetaxel an additional chemotherapy would be used before abiraterone, and because it was unlikely that an alternative to docetaxel would be used first line. This view was shared by the ERG's clinical advisors.

The NICE final scope identified best supportive care (BSC) and mitoxantrone (alone or in combination with prednisolone) as comparators. Elements of BSC could include prednisolone, radiotherapy, bisphosphonates, analgesics, and radiopharmaceuticals. The manufacturer's scope indicated that no studies could be found that compared abiraterone with mitoxantrone, and that in the absence of evidence for any survival benefit from mitoxantrone in mCRPC, the survival of mCRPC patients given second line mitoxantrone would be assumed to be the same as that from BSC.

The manufacturer and NICE scopes mostly concurred regarding outcomes. However, whereas NICE itemised merely "Progression-free survival" (PFS), the manufacturer mentioned three methods for estimation of PFS, including time to treatment discontinuation, which in the economic modelling undertaken by the manufacturer was used as a proxy for PFS. The ERG's clinical advisors confirmed

that there were particular difficulties in estimating time to progression in mCRPC and they considered the use of time in treatment as proxy for PFS to be a reasonable choice in difficult circumstances.

The manufacturer's scope for economic analysis conformed to the requirements of the NICE base case. Of three subgroups identified by the NICE scope: baseline ECOG status, extent of prior taxane exposure, and time since taxane treatment, only ECOG status (ECOG 0/1 or ECOG 2) was listed by the manufacturer; the MS makes clear that analyses for NICE's other subgroup analyses were not available at the time of submission.

The manufacturer's scope identified end of life criteria as a special consideration for their submission. The NICE scope did not identify any special considerations.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence for the clinical effectiveness of abiraterone came from a multicentre double blind RCT (COU-AA-301) which compared abiraterone plus prednisone (or prednisolone) versus placebo plus prednisone (or prednisolone) in the treatment of mCRPC patients who had failed to respond during or after up to two prior chemotherapies of which at least one was docetaxel. Background supportive care therapies were allowed. Of 130 study centres 12 were located in the UK; other centres were located in W. Europe, N. America and Australia. Patients were stratified according to ECOG performance status, one or two previous chemotherapy types, and type of PC progression (PSA progression only, radiological progression in bone or soft tissue with or without PSA progression). Patients were randomised 2:1 to abiraterone + prednisolone / prednisone (AAP) or to placebo + prednisolone / prednisone (PP). Patients were excluded if they received surgery or local prostate intervention within 30 days of the first dose (AAP or PP) and patients with ECOG status >2 were excluded. The ITT population consisted of 797 and 398 receiving AAP and PP respectively. Nearly all patients were white (93%) and 90% had bone disease at entry. The OPC sub-population was pre-specified and contributed ~70% of the total; amongst the remaining 30% who received two different chemotherapy regimens one regimen was docetaxel.

1.2.1 Primary outcome

The primary outcome was overall survival (OS), the time from randomisation to death from any cause. A primary analysis was conducted after 552 deaths (12.8 months median follow up), and a subsequent updated analysis after 775 deaths (20.2 months median follow up). The MS presented primary and updated analysis for the ITT population and updated analysis results for the OPC

population. According to the updated analysis the gain in median survival from abiraterone was 4.6 months for the ITT population and [redacted] months for the OPC population. Hazard ratios easily reached statistical significance in favour of abiraterone for both the ITT and OPC comparisons between AAP vs. PP and were consistently in favour of abiraterone across all subgroups analysed.

1.2.2 Secondary Outcomes

Study COU-AA-301 pre-specified three secondary end points: i) time to PSA progression (a 50% increase in PSA concentration); ii) time to radiological progression or death (progression-free survival; rPFS); iii) PSA response rate (the proportion of patients reaching a $\geq$ 50% decrease in PSA confirmed by a second measure at least 4 weeks later).

PSA was only measured until treatment discontinuation so that in any analysis of time to PSA progression, censoring was very high in both trial arms (68.1% and 69.8% AAP and PP respectively). The results are not summarised here.

Time to radiological progression was prolonged in the AAP group relative to PP group (median days to progression of 171 versus 110; ITT population) and the comparison between groups reached statistical significance according to both primary and updated analyses (HR 0.673 and 0.663 respectively; P <0.0001). The FDA medical review for abiraterone indicated that most events in the rPFS analysis were deaths rather than monitored radiographic progression.[1] The ERG's clinical advisor confirmed that estimating rPFS in prostate cancer poses particular difficulties of interpretation.

The third pre-specified secondary outcome, PSA response rate, indicated statistically significant superiority of AAP relative to PP (in the primary analysis of the ITT population 29.1% responders versus 5.5% P<0.0001; and in the updated analysis [redacted]).

1.2.3 Additional effectiveness outcomes reported

Time to treatment discontinuation represents an important additional outcome because the manufacturer argues that this is the most reasonable available indicator of disease progression. For both ITT and OPC populations time to discontinuation was significantly extended for the AAP group relative to the PP group (by [redacted] months for the OPC population according to the updated analysis; hazard ratio: [redacted]).

The MS presented updated analyses for three patient reported outcomes (PROs): brief fatigue inventory short form (BFI), brief pain inventory short form (BPI) and Functional Assessment of Cancer Therapy-Prostate (FACT-P). These indicated that a statistically significant greater proportion of patients improved in the AAP arm than in the PP arm for all three measures and that there was no difference in the proportions deteriorating. However, the time to deterioration was significantly extended for the AAP arm relative to the PP arm (P values for hazard ratios for all three outcomes < 0.01).

The MS presented objective tumour response rates according to RECIST criteria, these were statistically significant and in favour of abiraterone (15% response versus 3% response, ITT population, updated analysis data)

Unplanned medical resource use (MRU) during the progression-free state was reported in terms of cost as £2,919.10 per patient for the AAP and £2,866.30 for PP. The manufacturer suggests that these costs were similar despite longer duration of PFS for AAP treatment because most costs are incurred shortly before progression (i.e. treatment discontinuation) which occurs for all patients.

[redacted]

1.2.4 Safety

The abiraterone acetate arm had a lower incidence of Grade 3 or 4 adverse events (AEs), serious AEs, AEs leading to discontinuation and AEs leading to death compared to the placebo prednisolone arm. Three AEs were identified that the manufacturer considered might occur more frequently in the AAP group:

[redacted].

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The submission appears to be complete in that it included the only RCT comparing abiraterone plus prednisolone with placebo plus prednisolone (study COU-AA-301) for mCRPC patients who had failed to respond during or following docetaxel therapy, and presented a systematic review looking for evidence that might allow an indirect comparison of the effectiveness of abiraterone versus mitoxantrone. COU-AA-301 was a double blind study reporting the objective outcomes of all-cause mortality and time to radiological progression or death. The COU-AA-301 trial provided persuasive evidence that abiraterone confers a survival advantage, increasing median survival by about 4 to 5 months. The effect was consistent across subgroups, however Black and other racial groups were underrepresented in the trial population and it cannot be certain that the effect is necessarily generalizable to these groups.

The submission took the view that only patients who had received docetaxel, and no additional types of chemotherapy for mCRPC, represented the most appropriate population for the decision problem, since these patients correspond to the licensed population and to the patients likely to receive abiraterone in the UK. This "one-prior chemotherapy" population did not correspond precisely with the COU-AA-301 trial population. Some patients in the trial (30%) had received docetaxel plus another type of chemotherapy. However randomisation was stratified by whether patients had received one or two types of prior chemotherapy. The submitted clinical evidence and economic analysis focussed on the one-prior chemotherapy subgroup within the trial. The selection of a trial subgroup for analysis reduced statistical power for comparison of outcomes between treatment arms.

Some subjective outcomes were reported, these favoured abiraterone relative to placebo.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer presented results generated from a de novo model.

The base case ICER when AAP was compared with PP was £52,851/QALY and was £46,617/QALY when AAP was compared to mitoxantrone. Various deterministic and probabilistic analyses resulted in ICERs between £48,451/QALY and £57,298 in PP comparisons and between £42,548/QALY and £50,537/QALY for MP comparisons.

[redacted].

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The manufacturer assumed that treatment discontinuation determined the transition between progression-free and progressed states. The most influential drivers for the manufacturer's estimates of the ICERs for abiraterone versus PP and mitoxantrone were the utilities attached to the progression free-state and the progressed state, and the difference between these.

The progression free and the progressed state utilities were taken from different sources. For the former, the manufacturer developed an algorithm relating FACT-P scores to EQ-5D scores using data for mCRPC patients held in a European PC registry containing some UK patients. Using this algorithm the progression-free patients in the COU-AA-301 study were assigned a utility of [redacted]. FACT-P was not monitored after treatment discontinuation. A utility of 0.5 for the progressed state was therefore taken from a published Scandinavian study[2] identified from a literature search. This value is lower than that for COU-AA-301 patients at end of treatment ([redacted] and [redacted] for PP and AAP arms respectively, based on algorithm and observed FACT-P scores).

The manufacturer undertook a regression analysis using FACT-P data from progression-free patients in the COU-AA-301 trial to explore the relationship between utility, treatment and baseline utility. This delivered an incremental utility of [redacted] in favour of abiraterone for a treatment effect. The resulting utility applied for AAP patients during the progression-free phase was therefore [redacted]. The mean age of COU-AA-301 patients receiving abiraterone was 69.1 years. The ERG notes that a utility value of [redacted] is similar or higher than that for similarly aged men in the general population, which may be implausible. These utility values imply utility decrements for the move off treatment of [redacted] for AAP and [redacted] of PP. However the ERG has some concerns regarding the manufacturer's approach to the regression; in the absence of access to individual patient data, the ERG's exploration of alternative approaches was necessarily limited. For a given utility for the progressed state this will tend to worsen the cost effectiveness of abiraterone. In the cabazitaxel STA for NICE[3] second line treatment of mCRPC the manufacturer calculated the utility of the progressive disease state by applying a decrement derived from the literature[4] to the utility value of stable disease. This decrement was 0.070 (0.085 was used in sensitivity analysis). In comparing these values with those used in the abiraterone model the ERG notes that the latter ([redacted] for AAP and [redacted] for PP) appear quite large. To estimate utility for the progression-free state the cabazitaxel STA made use of EQ-5D data

collected during an Early Access Programme for cabazitaxel-treated mCRPC UK patients. The actual value is CIC, however the cabazitaxel ERG remarked that it was close to a literature value of 0.715.[4]

For the economic base case, the manufacturer modelled overall survival (OS) using raw Kaplan-Meier (KM) data until 10% of patients remained at risk and then used an exponential extrapolation to predict survival during the "unobserved" part of the 10 year time horizon. The choice of a 10% at risk "cut off" before extrapolation is an arbitrary one, however the manufacturer undertook sensitivity analysis with a 5% cut off and found this had little effect on the resulting ICERs for AAP versus PP and AAP versus mitoxantrone, each of which were raised by 2.5% relative to base case. The ERG undertook further sensitivity analyses around the OS cut-off, across a range of 0% to 20%. The ERG notes that a 10% cut-off used by the manufacturer delivered a relatively low ICER amongst other cut-offs. Because the form of the exponential extrapolation depends on the hazard at cut-off it follows that this is also arbitrary. By using raw KM data for the observed part of OS (up to cut-off) the manufacturer takes into account all time points for events, however for extrapolation this approach is abandoned and only two time points are used (baseline and cut-off hazards). The ERG considers this inconsistency less reasonable than informing the extrapolation with all available event data points when a parametric distribution is fitted to the data. The ERG considers that the use of KM raw data may represent over-fitting and could be less appropriate than employing well-fitting parametric distributions (in this case Weibull). The rationale underpinning the use of cut-off, was that the tail of the KM data was associated with considerable uncertainty so that the resulting ICER estimates were unlikely to be reliable. The KM plots presented in the submission lacked 95% CIs; however the confidence intervals associated with each 21-day cycle point estimates for overall survival were available to the ERG from within the electronic model, and from this the ERG note that uncertainty associated with KM data beyond 10% of patients remaining at risk was appreciable.

The exponential extrapolations beyond 10% remaining at risk for overall survival in the COU-AA-301 trial AAP and PP arms fitted less well to the observed survival data than did Weibull parametric fits, especially so for the AAP arm (Appendix 7). For this reason and others described above, the ERG is of the opinion that on balance a more preferred choice for the base case model would be to use Weibull parametric fits rather than the exponential extrapolation selected by the manufacturer. However it is conceded that both models are based on data associated with considerable uncertainties. In contrast to the constant hazard extrapolation the Weibull fit imposes monotonically increasing hazard beyond the observed data so that abiraterone ceases to deliver survival gain relative to placebo beyond 5.47 years (Appendix 7), whereas with the constant hazard model abiraterone continues to deliver survival gain relative to placebo for up to 10 years. The manufacturer has commented on page 97 of the submission that "*Data from other mCRPC studies[11, 12, 29, 56] support an assumption of a monotonically increasing hazard, such a Weibull function*". When Weibull fits were used (other input

as base case) the ICERs were raised by 6.9% relative to the base case for both AAP versus PP and AAP versus mitoxantrone (to £56,484/QALY for the former and to £49,817 for the latter).

During the clarification process, the manufacturer supplied AIC and BIC values together with parameters for six distributions (Weibull, exponential, Gompertz, loglogistic, lognormal and gamma) fitted to the trial KM curves for overall survival. On the basis of AIC / BIC values a Weibull distribution was most suited to overall survival in the AAP arm while a lognormal was best for the PP arm. The manufacturer rejected the lognormal fit because it exhibited a long tail that generated a proportion of patients with clinically implausible long survival. The ERG explored lognormal fits for overall survival and found that the lifetime gain from abiraterone over BSC continued to rise beyond the 10 year time horizon. Such an advantage was not considered to be plausible and therefore the ERG agree with the manufacturer that for overall survival the Weibull distributions for both arms were the most appropriate. Using the same parametric distribution for both arms is consistent with advice within the NICE DSU document "Undertaking survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data".[5]

Treatment discontinuation was used as a proxy for progression. According to ERG clinical advisors, this was reasonable because radiological imaging is relatively insensitive to progression of bone metastases and because soft tissue progression requires MRI scanning which would be infrequently undertaken for this population. The manufacturer adopted a similar approach in modelling time to progression as was used for overall survival, namely the use of raw KM data followed by exponential extrapolation. However, there was some inconsistency of approach, since extrapolation in the AAP arm was from a cut off when 5% of patients remained at risk, whereas for the PP arm only the KM data were used. Furthermore in the electronic model the KM data for this arm appeared to leave about 2% of patients in state of non-progression. For the PP arm the shape of the KM plot for treatment discontinuation was unusual, with a large proportion (~30%) of patients withdrawn from treatment over a narrow period of a few weeks at about 60 days into treatment. The ERG considers that this is unlikely to represent actual progression and that true progression is more likely represented by a smooth curve such as could be described with a parametric fit.

During the clarification process the manufacturer provided AIC and BIC values for parametric fits to treatment discontinuation. According to AIC scores a loglogistic distribution provided the best fit for both arms. For the AAP arm the AIC scores for loglogistic and Weibull fits were reasonably similar.

When the loglogistic distribution (manufacturer's parameters) was fitted to treatment discontinuation for the AAP arm of the trial, the resulting curve crossed the exponential extrapolation part of the overall survival curve (manufacturer's base case) so that some patients apparently retained the non-

progressed state after death, a clearly implausible circumstance. The same situation held with the Weibull fit for overall survival of the AAP arm. A modelling solution might be offered by forcing the time to discontinuation curve to follow that for OS from the point of cross over onwards. However, the ERG considers that a more reasonable approach would be to use Weibull distributions, for overall survival for the reasons outlined above, and also for treatment discontinuation since the loglogistic distribution for the AAP arm generates a clinically implausible prolonged state of progression for some patients. The ICERs under this scenario are £58,116/QALY and £51,279/QALY for AAP versus PP and versus mitoxantrone (with or without prednisolone) respectively.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- A good quality double blind RCT demonstrated a clear survival gain from use of abiraterone.
- The analysis of mature data for overall survival upheld the survival benefit first demonstrated in the early published analysis.
- The RCT provided evidence that abiraterone delayed disease progression.
- The economic model was appropriately simple and well matched to the decision problem.
- A [redacted] PAS was proposed [redacted] within the economic model.
- Abiraterone may be considered an innovative therapy and has been categorised as a new class of agent that adds a further layer to the options available for the hormonal control of mCRPC.
- The drug is orally administered and thereby potentially convenient for patients, clinicians and the NHS when compared with alternative cytotoxic agents requiring IV infusion.
- Abiraterone is unlikely to be associated with some of the adverse effects that can result from the use of cytotoxic therapies for this condition.
- The mapping of EQ-5D to FACT-P appears to have advanced available procedures and identified serious errors in the method previously available in the public domain. The FACT-P instrument is widely used in prostate cancer.
- A thorough systematic review was completed looking for evidence that might allow a network meta-analysis to be conducted to determine the effectiveness of abiraterone relative to the designated comparators.

1.6.2 Weaknesses and areas of uncertainty

- The greatest uncertainty concerns the attachment of utility scores for progressed and progression-free states used in the model. Although a novel algorithm was developed, this was only used for the progression-free state because the pivotal trial did not monitor FACT-P data after progression. This algorithm delivered a utility that appears rather high for the age group and disease condition concerned. The utility used for the progressed state was low, so that the decrement in utility passing from the progression-free to the progressed state was about four times that reported in the literature and also greater than that used in a concurrent STA looking at cabazitaxel as second line treatment for mCRPC.[3] This large decrement tends to favour abiraterone in any cost effectiveness analysis. It is also likely that the trial recruited the fittest patients from those eligible and willing to participate; the utility attached to the progression-free state might thereby somewhat overestimate that of patients who might routinely receive abiraterone.
- As far as monitoring of radiological progression in the RCT is concerned, it appears that either the trial investigators failed to scan an appreciable proportion of patients appropriately before they died or their scans were not analysed and used in the survival analysis of time to progression.
- There was a lack of detail in the original submission about reasons for hospitalisations in the trial; however this deficiency was satisfactorily rectified during the clarification process.
- The selection of the base case methods for modelling overall survival to the life time horizon tended to somewhat favour abiraterone relative to options considered more appropriate by the ERG.
- There was some uncertainty, within the model and in the MS, regarding how parametric distributions for modelling survival should be implemented.
- The algorithm used for mapping of EQ-5D to FACT-P scores has yet to appear in a peer reviewed publication.
- Although the MS investigated several parametric fits for survival data, the alternatives could not easily be implemented in the economic model. Some model rebuilding was required by the ERG so as to fully investigate parametric modelling of survival data.
- Details of the number of bone metastases for patients in the COU-AA-301 trial were not collected.
- The population most appropriate for the decision problem was a subpopulation within the pivotal trial. However this deficiency was offset to some degree, since that population was pre-specified as a stratum for randomisation.

1.6.3 Key issues

The main drivers of the economic model are the utilities attached to the progression-free and progressed states, together with the differential between these. The validity of these estimates is therefore a key issue for the submission and the ERG has a number of concerns about the derivation of these values as used in the manufacturer's model. Serendipitously, a concurrent STA of cabazitaxel for mCRPC patients who have failed to respond during or after docetaxel therapy also required estimates of utility for the same disease states in order to model cost effectiveness. These estimates are relevant for purposes of context and consistency and we have used them to assess possible different utility inputs to the model.

The MS argues that AA is an innovative therapy and that the application of end of life criteria are applicable. These represent key issues for consideration.

The abiraterone model employed treatment discontinuation as a proxy for progression; the reasonableness of this option may be questioned. A key issue is how clinically relevant this outcome is and what merit it has as an indicator of progression.

The active comparator identified for this appraisal was mitoxantrone, alone or in combination with prednisolone. The MS takes the view that mitoxantrone is barely used in the UK in this patient group and that the relevant comparator is BSC. The validity of this view is a key issue. In the absence of both a direct and an indirect evidence base for the comparison of effectiveness of abiraterone with mitoxantrone, another important issue is how reasonable is the manufacturer's handling of mitoxantrone inputs for the economic model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG opinion is that the most appropriate modelling for the base case is to apply Weibull fits for all the OS and PFS curves. Administration costs can be revised to reflect oncology follow-up reference costs, follow up chemotherapy administration costs for mitoxantrone, variation in average patient body surface area for mitoxantrone and a more realistic percentage of patients receiving bisphosphonates following progression. In addition further correction to reflect the manufacturer's regression analysis of the utility for progression free survival while receiving prednisolone results in:

- MP remaining extendedly dominated
- AAP conferring [redacted] QALYs at an additional cost of [redacted] to yield a cost effectiveness estimate of £60,084 per QALY.

The ERG has concerns about the appropriateness of applying a half cycle correction to the direct drug costs. Removing this would increase net costs by around [redacted] and further worsen the cost effectiveness by around £2,500 per QALY.

Additional sensitivity analyses from this revised baseline were undertaken by the ERG and are listed below. All resulted in an increased cost per QALY.

Additional sensitivity analyses from this revised baseline were undertaken by the ERG:

- Applying a truncated log normal curve for OS in the PP arm worsened the cost effectiveness to £70,217 per QALY.
- Applying an unplanned resource use of £106 per week for progression free survival, rather than the fixed cost of £2,800, worsened the cost effectiveness to £67,554 per QALY.
- Applying a fixed unplanned resource use cost for survival with progression, rather than the £95 per week, worsened the cost effectiveness to £60,492 per QALY.
- Applying a utility increment for on treatment with AAP over PP of [redacted] as drawn from a simple weighted average of the average post baseline FACT-P scores worsened the cost effectiveness to £65,911 per QALY.
- Applying a utility increment for on treatment with AAP over PP of [redacted] as drawn from a simple weighted average of the average post baseline FACT-P scores reported during the peak reporting periods worsened the cost effectiveness to £63,281 per QALY.
- Applying the utility increment of [redacted] as drawn from the PP baseline value, [redacted], minus the PP end of therapy value, [redacted], to the post progression utility of 0.500 to yield an on treatment utility of [redacted] worsened the cost effectiveness to £72,469 per QALY.
- Applying the PP end of therapy utility to survival with progression worsened the cost effectiveness to £63,326 per QALY.
- Adopting the approximate utility values from the cabazitaxel STA of 0.715 for progression free survival and 0.645 for survival with progression worsened the cost effectiveness to £67,140 per QALY.

2. BACKGROUND

This report provides a review of the evidence submitted by Janssen in support of abiraterone acetate (trade name Zytiga) for the treatment of metastatic castration resistant prostate cancer (mCRPC) after progression during or following docetaxel therapy. It considers the original manufacturer's submission (MS) received on 23rd September 2011 and the manufacturer's responses to clarification requests received on 2nd November 2011.

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of mCRPC following or during failure of docetaxel therapy is appropriate to the decision problem. The overview of the disease is given in section 2.1 of the MS and summarised below.

The manufacturer states that prostate cancer develops as a localised tumour following genetic mutations that override normal cell proliferation and differentiation controls.[6] Androgen deprivation therapy (ADT) slows tumour growth and delays progression. However, with further mutations, the tumour can become invasive and spread to surrounding tissues, including lymph nodes, distant tissues and organs including bone. The diagnosis of mCRPC is made when tumours spread outside the prostate, in spite of ADT therapy. The MS then refers to the European Association of Urology (EAU) guidelines which state that mCRPC is diagnosed by measuring serum levels of testosterone, increased level of prostate specific antigen (PSA) and radiographic progression of tumour lesions.[7] The ERG notes that according to NICE guidelines for prostate cancer (CG58), mCRPC is considered to exist '*when androgen withdrawal therapy or combined androgen blockade are no longer controlling the PSA or the symptoms of the disease, or when there is radiological evidence of progression*'.[8] The guideline also states that there is no definition for mCRPC.

The MS reports that the five-year survival rate is significantly worse in patients with distant metastases compared to localised disease (31% vs. 100%) however ERG notes that these data come from the US.[9] The ERG identified a report stating that the five-year survival for localised prostate cancer in England between 1999 and 2002 was 90% or more (a figure slightly different to that reported in the MS) whereas it was only around 30% for the metastatic disease.[10]

The MS Section 2.1 states that patients with metastatic disease may exhibit a variety of clinical symptoms including weight loss, lower extremity pain, and oedema due to obstruction of venous and lymphatic tributaries by nodal metastases.[11,12] Urethral obstruction can also occur and this leads to

uremic symptoms.[11] About 90% of patients with mCRPC have metastases to bone that may give rise to skeletal related events (SREs) or complications such as spinal cord compression or vertebral fractures and pain in up to 40% of patients.[12]

The manufacturer states that patients with metastatic disease suffer a substantial psychological burden because of the many symptoms associated with the disease and chemotherapy. The ERG found a systematic review conducted by Harrington and colleagues (2010) that conforms to the manufacturer's description.[13] The review explored symptom burden in survivors following primary treatment for PC. Patients with prostate cancer after treatment experienced a number of psychosocial symptoms. Some survivors had cognitive limitation, about 14% had clinical depression at one year and 17% at ~ two years, while estimates of depressive symptoms or emotional distress ranged from 26% (longitudinal studies) and 32% (cross sectional studies).[13]

Section 2.2 of the MS gives estimates of the population who will be eligible for abiraterone acetate treatment. The manufacturer first provides the NICE estimate of 10448 men[14] with mCRPC in England and Wales in 2006 and then uses 2011 population estimates[15] to calculate a current estimate. The MS states that currently there are 10,856 men with mCRPC and that this will rise to 11238 by 2016. The submission then estimates that about 40% of this population will receive treatment with docetaxel (i.e. 4400 men). This estimate was based on consultation with a group of UK clinicians in a process described in section 6.3.5 of the submission. The disease will progress despite docetaxel therapy in these patients. The submission estimates that 75% would subsequently be eligible for treatment with abiraterone acetate (i.e. 3,300 men). The estimate of 75% is based on the number of patients surviving treatment on docetaxel therapy at one year.[16]

The ERG is aware of a cabazitaxel submission currently being assessed by NICE.[3] The population under consideration in that submission is not different to the one considered here. The ERG notes that the number of estimated mCRPC patients in the cabazitaxel submission was significantly lower. In addition, contrary to the estimates in this submission, it was estimated that 50% of these patient will be eligible to receive first-line docetaxel therapy while only 55% of them will receive second-line chemotherapy. The estimates of 50% and 55% were based on market research commissioned by the manufacturer of cabazitaxel. These estimates are summarised in Table 1.

Table 1. Difference between estimate of mCRPC patients between Abiraterone and Cabazitaxel submissions

	Abiraterone submission	Cabazitaxel submission[3]
Incidence of mCRPC in England and Wales (NICE estimate in 2006)[14]	10,448	-
Incidence of mCRPC in 2011	10,856	7,047 (manufacturer's estimate); 6632 (ERG's estimate)
Eligible for docetaxel	40% eligible (4,400 men)	50% eligible [3,524 (manufacturer's estimate); 3,316 (ERG's estimate)]
Eligible for abiraterone acetate	75% of 4,400 mCRPC patients eligible (3,300 men)	55% fit for second-line chemotherapy (1938-manufacturer estimate; 1823 – ERG estimate)

The ERG notes that the MS estimate of 10,856 men with mCRPC in England and Wales exceeds the estimate in the cabazitaxel submission by 54% (i.e. 3,800 men). The estimate of 7,047 mCRPC patients in the cabazitaxel submission came from an epidemiological model developed by the manufacturer which was not made available to the cabazitaxel ERG. The MS estimate of 10,856 in this submission was based on the NICE estimate of 10,448 in 2006 equated to 2011 population estimates.

Similarly, there is contradiction between the two submissions in terms of the proportion of patients eligible for docetaxel or second-line chemotherapy. Using the figure of 7,047 (from cabazitaxel submission) and the estimates of 40% and 75% (from abiraterone submission), the proportion of patients eligible for docetaxel and abiraterone acetate would be 2,819 and 2,114 respectively. Similarly, using 10,856 (from abiraterone submission) and estimates of 50% and 55% (from cabazitaxel submission) then the proportion of patients eligible for docetaxel and abiraterone acetate would be 5,428 and 2,985 respectively. These differences are substantial.

It is worth noting that the NICE guidance on docetaxel for prostate cancer (TAG 101) was published in 2006 and was subsequently incorporated into the NICE Prostate Cancer guidelines on diagnosis and treatment in 2008 (CG58).[8] Details are given below:

Recommendations from NICE TAG 101 are as follows:

- *Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more.*
- *It is recommended that treatment with docetaxel should be stopped:*
    - *at the completion of planned treatment of up to 10 cycles, or*
    - *if severe adverse events occur, or*
    - *in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies.*
- *Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.*

Recommendation from the NICE Prostate Cancer guidelines (CG58)[8] relating to metastatic disease is as follows:

- *When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their treatment options should be discussed by the urological cancer multidisciplinary team (MDT) with a view to seeking an oncological and/or specialist palliative care opinion as appropriate.*

2.2 Critique of manufacturer's overview of current service provision

Section 2.4 of MS offers a view of the current treatment options for metastatic prostate cancer as outlined in the current NICE guidelines (CG58).[8] This is summarised in MS Figure 2 which is reproduced below (Figure 1):

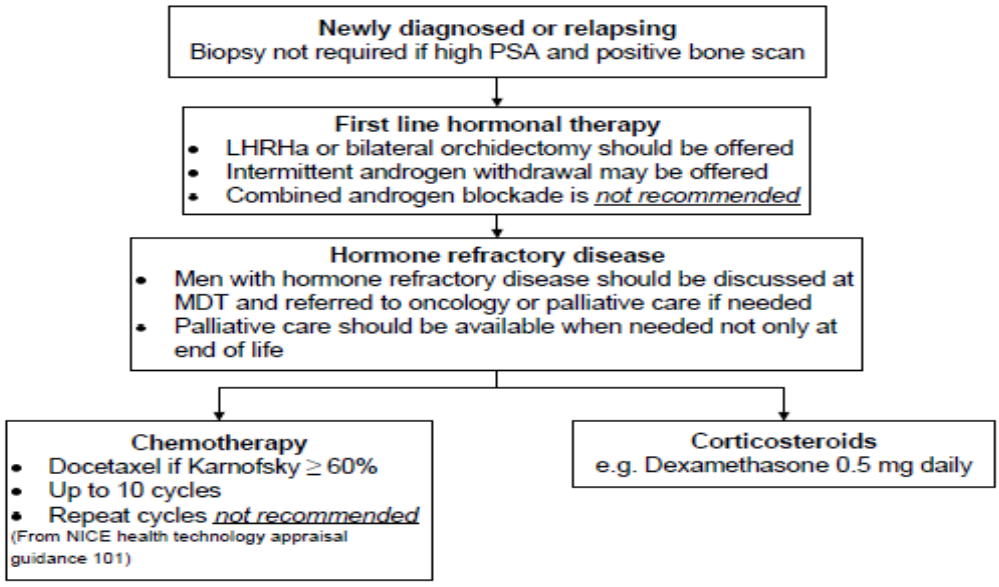


Figure 1. Prostate cancer algorithm for the treatment of metastatic disease (NICE guideline CG58)
[PSA: prostate specific antigen; LHRHa: luteinizing hormone-releasing hormone analogue; MDT: multidisciplinary teams]

The guideline recommends hormonal therapy (with an LHRH agonist) or bilateral orchidectomy as first line therapy. The hormonal therapy greatly reduces circulating testosterone levels which in turn provide temporary cessation of tumour growth. If medical castration (LHRH agonist treatment) fails then surgery (bilateral orchidectomy) is carried out. With time, all patients become refractory to first-line therapy.

Currently docetaxel in combination with prednisolone is the only chemotherapy regimen licensed in the UK as first-line treatment of mCRPC. A maximum of 10-cycles of docetaxel is recommended in

patients with a Karnofsky performance status score of 60% or more. Docetaxel plus corticosteroids is the only treatment with clinical evidence of delayed disease progression and improved overall survival (OS) for mCRPC.

The MS proposed that in the UK a very small proportion of mCRPC patients receive 2nd-line chemotherapy (10% docetaxel re-challenge, 10% mitoxantrone) while the majority (80%) receive best supportive care (BSC) which includes the use of chronic corticosteroids, palliative radiotherapy, oxygen, antibiotics, analgesics and bisphosphonates (Figure 2). Again these estimates came from a consensus meeting of clinicians convened by the manufacturer. The ERG's clinical advisor explained that BSC in UK includes good palliative care e.g. bone preservation advice (on weight, diet, exercise), 1st, 2nd and 3rd stage hormonal treatments, bone strengthening drugs i.e. bisphosphonates and self-management.

The MS states that the use of mitoxantrone after taxane failure is likely to be minimal as there is no evidence of a survival advantage. The ERG's clinical advisor concurred that in the UK there is currently very little use of mitoxantrone for mCRPC. The ERG notes that the cabazitaxel submission states: "*mitoxantrone is widely used in the UK even though it is not licensed, due to its established palliative benefits in mHRPC"*.

It is worth noting the cabazitaxel submission states that only 55% of the patient population will receive second-line chemotherapy.

The following figure, taken from the MS (Figure 3 of the MS, page 27), represents the manufacturer's view of the treatment pathway.

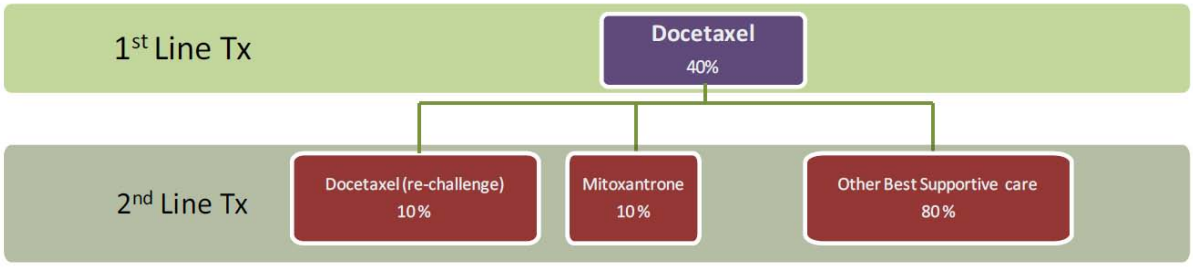


Figure 2. Current treatment pathway in mCRPC as determined by expert clinical opinion in the consensus meeting.

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem as issued by NICE and addressed by the manufacturer is given in section 4 of the MS. It is reproduced below (Table 2).

Table 2. Decision problem as issued by NICE and addressed by the MS

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

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

3.1 Population

The NICE scope specifies the population as men with mCRPC whose disease has progressed on or after docetaxel-based chemotherapy. The manufacturer's base case economic analysis focuses on a population termed the 'One Prior Chemotherapy' group. Clinical input parameters for this group were taken from a subgroup of patients in the pivotal RCT (COU-AA-301) that received one or more courses of docetaxel but no other type of chemotherapy regimen. The MS proposes that the 'One Prior Chemotherapy', closely reflects the population that will receive abiraterone acetate in England and Wales. The ERG's clinical advisor agreed with this view. The remaining patients in the COU-AA-301 trial received docetaxel and one other chemotherapy prior to abiraterone acetate.

3.2 Intervention

The MS anticipates that in the UK abiraterone acetate (trade name Zytiga) will be used in combination with prednisolone for patients with mCRPC whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The drug received a marketing authorisation in the EU (European Union) on 5th of September 2011 for use in combination with prednisone or prednisolone for treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.[17] It also received an FDA approval on 28th of April 2011.[18]

Abiraterone acetate is an orally taken drug for treatment of mCRPC that rapidly converts to a potent androgen biosynthesis inhibitor, abiraterone. Abiraterone selectively inhibits the enzyme 17α-hydroxylase (CYP17), which catalyses conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone (DHEA) and androstenedione. This will in turn block androgen biosynthesis at all sites in the body including testes, adrenal glands and prostate tumour.

The following information is based on the EMA SmPC.[19] AA is taken as a single dose of 1 gram (4 x 250 mg tablets) per day until disease progression (defined by progression of clinical symptoms and/or radiological assessment and/or PSA progression). The drug should be taken at least two hours after meals and no food should be eaten for at least one hour after taking the drug, as food increases systemic exposure to the drug. The recommended daily dose for prednisolone is 10 mg taken as 5mg twice daily. The cost of abiraterone acetate (excluding VAT) treatment for 30 days is £2,930. Abiraterone acetate is self-administered at home and is not associated with administration costs. Blood is monitored for serum transaminase levels prior to starting therapy, every two weeks in the first three months and then monthly thereafter. There is no need for dose adjustment in patients with pre-existing mild hepatic impairment but the drug should be avoided for patients with pre-existing

moderate or severe hepatic impairment. If patients on treatment develop hepatotoxicity then it should either be discontinued or dose adjusted. There is no need for dose adjustment in patients with renal impairment although caution is required in patients with severe renal impairment.

Abiraterone acetate may cause hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess however prednisolone counteracts these adverse events.

3.3 Comparators

The NICE final scope specifies the following comparators:

- Best supportive care (BSC) that may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies and corticosteroids
- Mitoxantrone alone or in combination with prednisolone

The manufacturer views BSC, constituted as use of chronic corticosteroids, palliative radiotherapy, oxygen, antibiotics, analgesics and bisphosphonates as the main comparator. Based on the advice of a clinical panel, the manufacturer has concluded that about 80% of the patient population will receive BSC and that the treatment received by patients in the comparator arm (PP) of the pivotal RCT (COU-AA-301) fairly reflects the BSC used in the United Kingdom. In the trial, patients in the control arm received placebo in combination with prednisolone and additional supportive care. Both treatment groups had the option of choosing the additional elements of supportive care listed below:

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

The ERG's clinical advisor confirmed that most patients with mCRPC in UK who have failed on or during docetaxel therapy will receive BSC which includes good palliative care e.g. bone preservation advice (on weight, diet, exercise); 1st, 2nd and 3rd stage hormonal treatments; bone strengthening drugs i.e. bisphosphonates and self-management.

The second comparator specified by NICE, mitoxantrone in combination with prednisolone, was not considered to be relevant by the manufacturer, however it has been included in order to comply with the scope. The clinician group suggested that only about 10% of the patient population in the UK are likely to receive mitoxantrone as a second line treatment. A further difficulty is the lack of an RCT

comparing mitoxantrone plus prednisonole against BSC (with prednisonolone) or against AAP in the relevant patient population. The ERG's clinical advisors were of the opinion that in the UK there is currently very little use of mitoxantrone for mCRPC.

The manufacturer did not include cabazitaxel, a semi-synthetic taxane as a further comparator since it is currently being considered by NICE in a separate STA.[3]

3.4 Outcomes

Overall survival (OS) and Progression-free survival (PFS) are specified as major outcomes by both NICE and the manufacturer. All the outcomes suggested by NICE are also specified by the manufacturer.

Definitions of all outcomes are given in the published paper[20] however for convenience they are reproduced below:

Overall survival: is Defined as the time from randomisation to death from any cause

PSA response rate: Defined as the proportion of patients with a reduction in PSA level of 50% or more from the baseline value, confirmed 4 weeks later by an additional PSA evaluation.

Time to PSA progression: Three sets of patients are described; 1) In patients whom the PSA level had not decreased, PSA progression was defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 ng per millilitre, which was confirmed by a second value, 2) In patients in whom the PSA had decreased but had not reached response criteria (PSA ≥50%), PSA progression considered if the PSA level increased 25% over the nadir, provided that the increase is a minimum of 5 ng/mL and is confirmed; 3) for patients who experienced at least a 50% decrease in the PSA, PSA progression required an increase of 50% above the nadir and ≥ increase of 5 ng per millilitre.

Radiographic evidence of progression-free survival: Defined as soft-tissue disease progression according to modified RECIST (baseline lymph node ≥2 cm to be considered target lesion) or progression by bone scans with ≥2 new lesions not consistent with tumour flare.

Pain palliation rate: Defined as a reduction in the BPI-SF worst pain intensity score by 30% or more over the last 24 hours observed at two consecutive evaluations 4 weeks apart without any increase in analgesic use. Patients experiencing a pain score of 4 or more at baseline were included.

3.5 Other relevant factors

The manufacturer declares that abiraterone acetate is the only available drug that can extend survival and delay disease progression in mCRPC patients whose disease has progressed on or after docetaxel based chemotherapy.

The manufacturer confirmed in clarifications that EoL criteria should be used to evaluate abiraterone acetate. Their reasons include a) prognosis among these patients is poor, b) patient population is small and c) abiraterone acetate offers a 4.6 months increase on median overall survival compared to placebo + prednisolone.

The ERG note that the discrepancy between cabazitaxel and abiraterone submissions identified regarding the number of mCRPC patients is not likely to affect this consideration since the population under consideration remains small.

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

4.1.1 Objective of the systematic review, and description and critique of the manufacturer's search strategy

The manufacturer carried out three searches, a full systematic search to identify all the relevant trials/studies of abiraterone acetate and potential comparators in patients with mCRPC following first-line taxane chemotherapy, a second systematic search to identify relevant cost-effectiveness studies, and a third systematic search to identify all HRQL publications relevant to mCRCP. In addition to the interventions outlined in the decision problem, other commonly used interventions for mCRPC were also included in the search strategy. A wide range of databases were searched including conference proceedings. The ERG believes that the three systematic searches carried out by the manufacturer are of good quality, although the ERG has a few minor criticisms of the search strategy as detailed in Appendix 5 (PRESS checklists[21]). The ERG believes that it is unlikely that any relevant studies have been missed.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection, and whether they were appropriate

The manufacturer gives details of inclusion/exclusion criteria and rationale for the same in Table 4 (section 5.2.1) of the MS.

The systematic review was limited to English language only. The manufacturer's view was that this would not substantially affect results.

The manufacturer's inclusion criteria appropriately allowed for current interventions for treatment of mCRPC and all aspects of BSC (palliative radiotherapy, corticosteroids, oxygen, analgesics, or placebo). The inclusion criteria appropriately allowed inclusion of observational studies that potentially might provide a real life effectiveness data. Appropriate justification was provided to exclude- subgroups of patients other than mCRPC, weak study designs such as case studies, case series and case reports, phase I and dose ranging studies.

Thus ERG believes that inclusion and exclusion criteria employed in the MS were appropriate.

4.1.3 Studies included in the clinical effectiveness review, with a table of identified studies

In section 5.2.2 of the MS, the manufacturer states that five abiraterone acetate studies in mCRPC post-chemotherapy patients were identified during systematic review - one RCT (COU AA-301) and three single arm studies (COU-AA-304, COU-AA-003, COU-AA-BMA). Details of these studies are given in the MS. For convenience, the two tables are reproduced below:

Table 3. List of relevant RCTs

Trial no. (acronym)	**Intervention**	**Comparator**	**Population**	**Primary study references**
COU-AAA-301 (NCT00638690)	Abiraterone acetate (1g q.d) + prednisolone (5mg b.i.d) until disease progression (AAP)	Placebo + prednisolone (5mg b.i.d) until disease progression (PP)	mCRPC patients whose disease has progressed during or after docetaxel-based chemotherapy	COU-AA-301 manuscript[20] Clinical Study Report COU-AA-301[22] Statistical Report of updated analysis of COU-AA-301[23] Analysis of patient reported outcomes data from COU-AA-301[24]

Table 4. List of relevant non-RCTs

Trial no. (acronym)	**Intervention**	**Population**	**Objectives**	**Primary study ref.**	**Justification for inclusion**
COU-AA-004 (NCT00485303) Single arm study	Abiraterone acetate (1g q.d) + Prednisone (5mg b.i.d)	mCRPC patients who experienced treatment failure with docetaxel	Single arm Phase II study to evaluate the efficacy and safety of AA in combination with prednisone to reduce the symptoms of secondary hyperaldosteronism in (n= 58)	Danila, Morris et al., (2009)[25]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 36% of patients
COU-AA-003 (NCT00474383) Single arm study	Abiraterone acetate (1g q.d)	CRPC patients with progressive disease and PSA >5ng/mL	Single arm Phase II study to evaluate the proportion of patients achieving a PSA decline of ≥50% (n=47)	Reid, Attard et al., (2010)[26]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 51% of patients
COU-AA-BMA (NCT00544440) Single arm study	Abiraterone acetate (1g q.d) + Prednisone	CRPC with baseline serum testosterone <50ng/dl (82% had prior chemotherapy)	To explore associations between serum (endocrine) and microenvironment (paracrine) androgen concentration and response to abiraterone acetate (n=17)	Logothetis, Wen et al.,(2008)[27]	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 41% of patients
		Progressive CRPC patients (61% with 2 or more chemotherapies)	Single arm study to explore the predictive benefit of an "intracrine androgen signalling signature " in patients treated with abiraterone acetate plus prednisone (n=56).	Efstathiou, Tu et al., (2010)[28] (ASCO) presentation	This single arm, Phase II study is supportive data demonstrating efficacy and tolerability of abiraterone acetate. PSA response (≥50% decline) was confirmed in 46% of patients

The manufacturer's clinical effectiveness evidence comes from only one randomised clinical trial – COU-AA-301, wherein abiraterone acetate in combination with prednisolone was compared against placebo plus prednisolone in patients with mCRPC who had progressed on or after docetaxel therapy.

4.1.4 Details of relevant studies not discussed in the MS

The ERG is not aware of any other relevant studies in mCRPC patients whose disease has progressed after or on docetaxel therapy which were not discussed in the MS.

4.2 Summary and critique of submitted clinical effectiveness evidence

4.2.1 Summary of submitted clinical evidence for each relevant trial

The clinical evidence comes from the manufacturer funded phase III, double-blind, multicentre, multinational RCT, COU-AA-301, in which mCRPC patients whose disease has progressed during or after docetaxel-based chemotherapy received abiraterone acetate in combination with prednisolone (AAP) or placebo plus prednisolone (PP).

Data from the 'Primary analysis' comes from both published[20] and unpublished sources i.e. CSR and an analysis of the PRO (patient reported outcomes) data. Data from the 'Updated analysis' comes from the Statistical Report (unpublished) supplemented by additional analyses presented at ASCO in 2011 and an analysis of the 'Updated' PRO data.

The ERG did not find any other relevant studies.

4.2.2 Description and critique of the manufacturer's approach to validity assessment for each relevant trial

The trial appeared to be of high quality. The ERG's quality assessment according to the Cochrane Collaboration risk of bias criteria[29] is produced in Appendix 1.

The submission states:

[redacted][a]

[a] This is important because in the economic modelling treatment discontinuation is used as the main marker for transition from progression-free survival to progression.

[redacted]. It is relevant to note that FDA carried out an inspection of five sites (2 in UK, 1 in Italy and 2 in US) to validate reliability of the trial data.[1] The reasons to undertake this inspection were stated as follows: "*a) Regulatory action for this application depends solely on the results from a single Phase 3 trial halted prior to its completion and planned final analysis due to the IDMC recommendation that the pre-specified interim analysis had demonstrated an improvement in overall survival in the abiraterone treatment arm compared to placebo arm; b) the Applicant identified that original sites monitoring was inadequate, which then necessitated their undertaking an extensive re-monitoring program to ensure the reliability of data submitted".* During inspection of all five inspected sites, the FDA's DSI (Division of Scientific Investigation) found a few minor discrepancies and these were considered not to be significant. Therefore the FDA concluded that the data were reliable and issues impacting on the reliability of the data were not present.[1]

The ERG has minor concerns about the generalisability of the COU-AA-301 results since only 12 of the 130 study centres were in the UK, and because nearly all patients (> 90%) in the trial were white (only 3.6% and 1.8% were Black and Asian respectively).

4.2.3 Description and critique of the statistical approach used within each relevant trial

The statistical analyses used in the COU-AA-301 trial are summarised in Table 11 and section 5.3.6 of the MS. The ERG believes that the statistical tests carried out by the manufacturer were appropriate.

Subgroup analyses

The following subgroup analyses were planned for the primary endpoint OS to assess whether treatment effects were consistent across subgroups:

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

In addition to the above pre-specified subgroup analyses, the following were also carried out:

- ECOG performance status score: 0-1 versus 2
- Pain: BPI <4 or ≥4
- Number of prior chemotherapy regimens: 'One Prior Chemotherapy' versus 2 or more different types of prior chemotherapy
- Baseline age (<65, ≥65, ≥75 years)

The MS includes results for pre-specified subgroups analyses using primary analysis data. In addition, during the clarification process the manufacturer provided results for subgroup analyses using updated analysis data.

4.2.4 Description and critique of the manufacturer's approach to outcome selection within each relevant trial

The following outcomes were listed in the MS.

- Primary outcome: OS
- Secondary outcomes:
    - Time to PSA progression based on PSAWG criteria,
    - PSA response rate,
    - rPFS
- Other outcomes
    - mPFS,
    - Objective tumour response,
    - Pain palliation,
    - Time to pain progression,
    - Fatigue progression,
    - QoL total score and each subscale score as assessed by FACT-P,
    - Time to first SRE,
    - CTC response rate,
    - Adverse events and serious adverse events,
    - MRU information

The outcomes pre-specified in the NICE final scope and the submission were mostly similar. In the MS, progression free survival (PFS) mentioned in the NICE final scope, has been described using three different outcome measures namely a) radiographic PFS (rPFS), b) modified PFS (mPFS) and c) time to treatment discontinuation. The latter has been used as a proxy for PFS in the economic

modelling. The ERG's clinical advisors confirmed that ascertaining disease progression using radiological images is difficult as patients may die without any evidence of radiological progression (bone metastasis not sensitive to change). Therefore, they considered it to be acceptable to use time to discontinuation as a proxy for PFS in difficult circumstances.

Although the manufacturer pre-specifies outcomes as primary and secondary endpoints in the tabulated decision problem, in the MS text it was difficult to determine if a specified secondary outcome or additional outcome was the subject of discussion.

4.2.5 Discussion of the extent to which relevant trial includes the patient population (s), intervention (s), comparator (s) and outcomes as defined in the final scope

The MS defines all the patients in the pivotal COU-AA-301 trial as the ITT population. Although this ITT population is similar to that defined in the final scope (i.e. men with mCRPC whose disease has progressed on or after docetaxel based therapy), the submission has refined the population appropriate to the decision problem as a 'One Prior Chemotherapy' (OPC) population defined as those patients who have received only docetaxel chemotherapy. In the COU-AA-301 trial about 70% of patients received only docetaxel while remaining patients received more than one type of chemotherapy. The manufacturer considers that the OPC population, rather than the ITT population, more closely reflects those mCRPC patients in England and Wales most likely to receive abiraterone acetate, because very few UK patients currently receive subsequent chemotherapy after first line docetaxel. The ERG's clinical advisors confirmed that second line chemotherapies are rarely used for patients with mCRPC who have failed to respond during or after docetaxel.

The intervention defined in the final scope was abiraterone acetate in combination with prednisolone (AAP) and this was evaluated in the COU-AA-301 trial.

In the NICE scope two comparators were defined: a) BSC and b) mitoxantrone alone or in combination with prednisolone (M or MP). The manufacturer explained that patients in the PP arm of the COU-AA-301 trial received treatment reflective of best supportive care in the UK since in addition prednisolone they also received supportive care that included radiotherapy, bisphosphonates, LHRH agonists as needed.

The active comparator specified in the NICE scope was mitoxantrone (M or MP); the MS points to the lack of comparative studies giving information on the effectiveness of M or MP versus AAP and to a systematic review demonstrating a lack of effect of M or MP on overall survival. Due to this lack of evidence the MS argues that the most appropriate representation of an M / MP treated population is

provided by the PP arm of the COU-AA-301 trial. The ERG's advisors confirmed that in the UK mitoxantrone is very rarely used in this patient population.

The COU-AA-301 trial included all the outcomes defined in the final scope. The scope did not classify outcomes as primary, secondary or other, however this was done in the MS. The three secondary endpoints were: i) time to PSA progression; ii) rPFS and iii) PSA response rate. (further details are provided in section 4.2.4).

4.2.6 Description and critique of any meta-analysis, indirect comparisons and/or mixed treatment analysis carried out by the manufacturer

Only one relevant trial (COU-AA-301) of abiraterone acetate was identified therefore it was not possible for the manufacturer to carry out a meta-analysis.

The manufactured did not undertake a network meta-analysis of comparators. The systematic review undertaken clearly revealed that there was a lack of direct and indirect evidence to link the comparators of interest in the post-chemotherapy patient population. The manufacturer's schematic network diagram, Figure 13 in the MS, has been reproduced below (Figure 3).

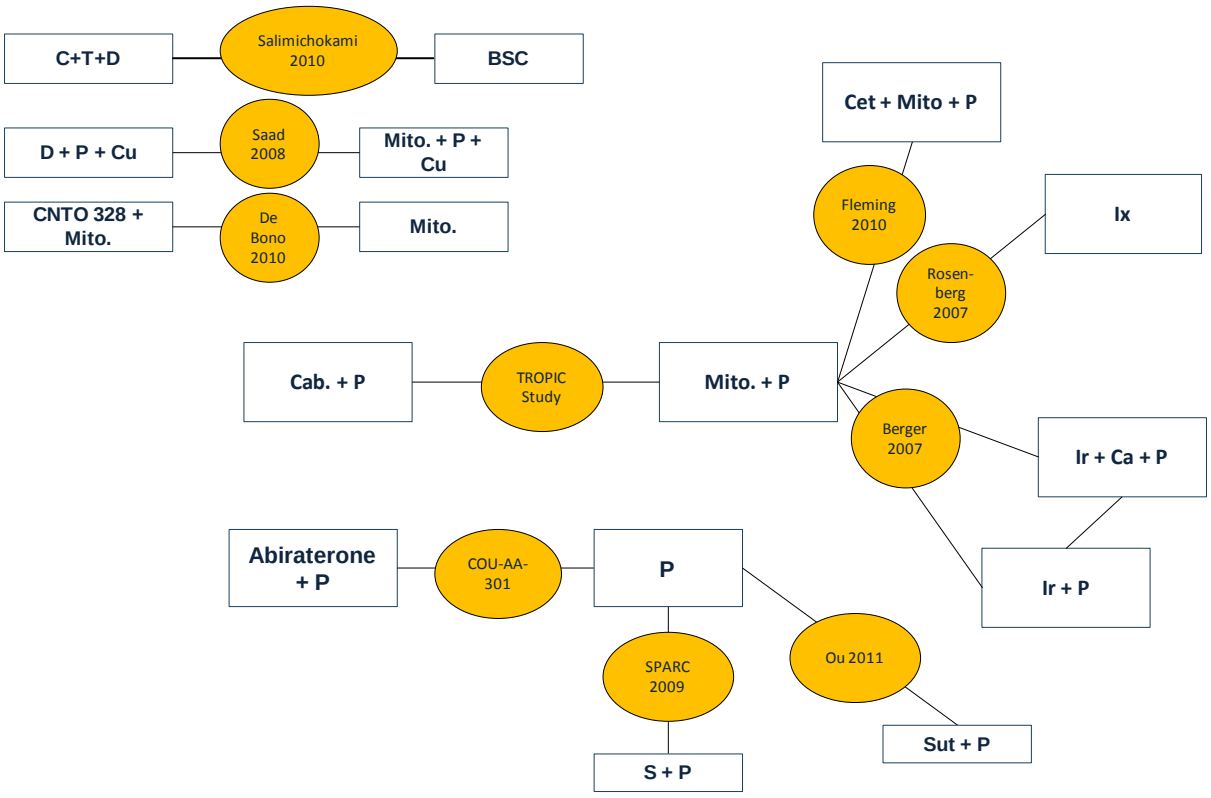


Figure 3. Schematic of the network of RCTs identified by the systematic review.

Key: BSC = Best supportive care; Cab. = cabazitaxel; Ca = capecitabine; Cet = Cetuximab; C+T +D = Cyclophosphamide + Thalidomide + dexamethasone; Cu = custirsen; D = docetaxel; Ir = ixabepilone; Mito. = mitoxantrone; P = prednisolone; S = satraplatin; Sut = sunitinib

Four RCTs[12,30-33] were identified that compared mitoxantrone + prednisolone with other drugs, however there was no trial in the network to link this evidence and compare against abiraterone acetate. The manufacturer identified three RCTs[34-36] of mitoxantrone + corticosteroids (prednisolone or hydrocortisone) versus corticosteroid in chemotherapy naïve patients; these showed no survival gain attributable to mitoxantrone. It was assumed to be highly unlikely that an intervention with no survival gain in first line therapy would provide survival benefit when used as second line treatment. The MS states that this information was supported by the group of clinicians consulted. Different assumptions around OS, PFS and palliative benefits of mitoxantrone have been explored in sensitivity analyses in the economic model.

4.2.7 Summary and Critique of effectiveness Results reported from the COU-AA-301 study

This section summarises the main clinical evidence from the COU-AA-301 study as reported in the MS, in the clarification responses to ERG queries and in FDA[1] and EMA[17] documents. Where possible, emphasis is placed on data for the OPC population according to the updated analysis, as this appears most appropriate for the decision problem.

Primary outcome: Overall survival.

The primary outcome was overall survival (OS), the time from randomisation to death from any cause. AAP provided an overall survival benefit relative to PP. A primary analysis was conducted after 552 deaths (12.8 months median follow up), and a subsequent updated analysis after 775 deaths (20.2 months median follow up). The MS presented primary and updated analysis for the ITT population and updated analysis results for the OPC population. The ITT updated analysis confirmed the primary analysis. MS Fig 9, shows the Kaplan Meier updated analysis for the OPC population ([redacted]).

The overall survival results presented in the MS are summarised below in Table 5.

Table 5. Primary and Updated analysis for the ITT and the OPC population

PRIMARY ANALYSIS								
Treatment arm	ITT population				OPC population			
	N	Deaths n (%)	Median (95% CI)	HR* (95% CI)	N	Deaths (%)	Median (95% CI)	HR (95% CI)
AAP	797	333 (42%)	14.8 (14.1 - 15.4)	0.646 (0.543 – 0.768)	[redacted]	NR	NR	NR
PP	398	219 (55%)	10.9 (10.2 -		[redacted]	NR	NR	

			12.0)					
		difference	*3.9 mos*			*difference*	*NR*	
UPDATED ANALYSIS								
AAP	797	501 (63%)	15.8 (14.8 – 17.0)	0.74 (0.638 – 0.859)	[redacted]	NR	[redacted]	[redacted]
PP	398	274 (69%)	11.2 (10.4 – 13.1)		[redacted]	NR	[redacted]	
		difference	*4.6 mos*			*difference*	[redacted]	

AAP = abiraterone + prednisolone; PP = placebo + prednisolone; ***** HR hazard ratio AAP versus PP by stratified proportional hazards model. mos = months

According to the updated analysis the gain in median survival from abiraterone was 4.6 months for the ITT population and [redacted] months for the OPC population. Hazard ratios for overall survival easily reached statistical significance in favour of abiraterone for both the ITT and OPC comparisons between AAP vs. PP.

The effect of abiraterone was consistent across subgroups. Pre-specified subgroup analyses, and analyses according to stratification subgroups used at randomisation, compared hazard ratios between treatment arms using the primary analysis data. These demonstrated a consistent and statistically significant effect in favour of abiraterone except for the small subgroup with ECOG status >1 where the HR point estimate was 0.81 with a 95% UCI >1.0 (compared with 0.64 for the subgroup with ECOG status 0 or 1). During the clarification process subgroup results calculated using the updated analysis data were provided; point estimates for HR for all subgroups were in favour of AAP and indicated [redacted] for the ECOG subgroups ([redacted] and [redacted] respectively for ECOG 0/1 and ECOG 2), although with the more mature data the HR for a few subgroups failed to reach statistical significance.

Progression free survival (PFS)

Radiological progression-free survival (rPFS) was a pre-specified secondary outcome and was "*based on imaging assessment of soft tissues (according to modified RECIST criteria)"* (MS Table 10) and undertaken every 3 weeks and at treatment discontinuation.

According to the primary analysis of the ITT population rPFS in the AAP arm was prolonged relative to the PP arm (HR 0.673; 95% CI: 0.585, 0.776, p <0.0001) and also according to the updated analysis ([redacted]). Median rPFS was the same in both primary and updated analyses: 171 days and 110 days in AAP and PP arms respectively.

The FDA medical review[1] for abiraterone provided the following results for PFS based on imaging in study COU-AA-301 (Table 6)

Table 6. Distribution of PFS events at the Interim Analysis

	AAP	PP
	(N=797)	(N=398)
Total PFS Event (%)	577 (72%)	327 (82%)
Death	333 (42%)	219 (55%)
Radiographic Progression	244 (30%)	108 (27%)
Censored (%)	220 (28%)	5 (18%)

Most events were deaths rather than monitored radiographic progression. Potential explanations include: (i) for many patients death followed very closely upon progression so that imaging missed the time of progression (this appears unlikely for most since the difference in medians between survival and rPFS was substantial, e.g. AAP arm 14.8 months and 5.6 months respectively); (ii) investigators did not perform imaging at the planned time intervals; (iii) imaging results were not processed sufficiently for incorporation into the analysis; (iv) radiological progression is difficult to establish. The ERG's clinical advisor confirmed that estimating rPFS in prostate cancer poses particular difficulties of interpretation.

Several measures of time to progression were presented in the MS in the New England Journal of Medicine publication describing results from the COU-AA-301 trial[20] and in the clarification responses provided by the manufacturer. In addition to rPFS these included: time to treatment discontinuation; time to PSA progression (a pre-specified secondary outcome); a modified PFS (based on time to death or one of the following: PSA progression, radiographic progression, increase in glucocorticoid use, pain progression, a SRE, or initiation of a new cancer therapy); pain progression. The results for these outcomes are illustrated in the manufacturer's Kaplan Meier analyses supplied as clarification Figures 2 and 3 which are reproduced in Appendix 3 of this report. The considerable disparity between different measures serves to illustrate the difficulty of finding a definitive measure for progression in mCRPC. Since PSA was only measured until treatment discontinuation the analysis of time to PSA progression involved very high levels of censoring in both trial arms (68.1% and 69.8% AAP and PP respectively) making the interpretation of results difficult.

Time to treatment discontinuation represents an important post-specified outcome because the manufacturer argues that this is the most reasonable available indicator of disease progression. For both ITT and OPC populations time to discontinuation was significantly extended for the AAP group relative to the PP group (results are summarised in Table 7).

Table 7. Results of time to treatment discontinuation for ITT and OPC population (months)

PRIMARY ANALYSIS						
Treatment arm	ITT population			OPC population		
	N	Median (95% CI)	HR (95% CI)	N	Median (95% CI)	HR
AAP	797	[redacted]	NR	[redacted]	NR	NR
PP	398	[redacted]		[redacted]	NR	
difference		[redacted]		*difference*	*NR*	

UPDATED ANALYSIS											
AAP	797	[redacted]									
PP	398	[redacted]									
difference		[redacted]			*difference*						
AAP = abiraterone + prednisolone; PP = placebo + prednisolone; mos = months											

The Kaplan-Meier analysis of time to treatment discontinuation for the OPC population using the updated analysis data was illustrated in MS Figure 12. The curve for the PP arm is characterised by a large proportion of patients (~30%) discontinuing over a short period (~3 weeks) around 16 weeks into the trial. While this synchrony of withdrawal of treatment can be assumed accurate, it may not reflect true disease progression which intuitively might be expected to follow a smooth trajectory. This issue has some relevance to how PFS for the PP arm is modelled for the economic analysis.

PSA response rate

PSA response rate (the proportion of patients reaching a ≥ 50% decrease in PSA confirmed by a second measure at least 4 weeks later) was a pre-specified secondary end point for study COU-AA-301. A statistically significant superiority for AAP relative to PP was reported with 29.1% responders versus 5.5% P<0.0001 (primary analysis, ITT population); in the updated analysis there were [redacted] in the PP arm; [redacted]).

Patient reported outcomes

The MS presented updated analyses for three patient reported outcomes (PROs): brief pain inventory short form (BFI-SF), brief fatigue inventory short form (BPI-SF) and Functional Assessment of Cancer Therapy-Prostate (FACT-P). These indicated that a statistically significant greater proportion of patients improved in the AAP arm than in the PP arm for all three measures and that there was no difference in the proportions deteriorating, however the time to deterioration was significantly extended for the AAP arm relative to the PP arm (P values for hazard ratios for all three outcomes < 0.01). The manufacturer proposes that these results indicate that "*men receiving abiraterone are more likely to experience reduced pain, improved functional status and decreased fatigue and have more time before their pain, functional status and fatigue worsens.*"

Tumour response rate

The MS presented Objective tumour response rates according to RECIST criteria, these were statistically significant, and in favour of abiraterone (15% response versus 3% response, ITT population updated analysis data); the results are summarised in Table 8.

Table 8. Results of objective Tumour response rates

PRIMARY ANALYSIS			
Treatment arm	N	Number with measurable disease	% with partial response
AAP	797	393*****	14%
PP	398	181*****	2.8%
P for comparison <0.0001			
UPDATED ANALYSIS			
AAP	797	NR	[redacted]
PP	398	NR	[redacted]
P for comparison <0.0001			

***** numbers taken from the FDA medical review AAP = abiraterone + prednisolone; PP = placebo + prednisolone; mos = months

4.2.8 Medical Resource use (MRU)

The MS clinical effectiveness section reported unplanned MRU in terms of cost. For hospitalisation while on treatment the

[redacted]

During the clarification process the manufacturer supplied data for the number of hospitalisations recorded for the OPC population while on treatment. This information is summarised in Table 9.

Table 9. Hospitalisation for OPC population

	Number of patients at risk	Median treatment duration (days)	Number of ICU hospitalisations	Number of non-ICU hospitalisations	Total number of hospitalisations
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ratio AAP/PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICU = intensive care unit

There appeared to be little difference between AAP and PP trial arms. The reasons for hospitalisation were also provided. Again the ERG could not identify any major differences between groups that might impact upon resource use. The MS stated:

[redacted]

Appendix 16 of the MS explains that

[redacted] Two analyses were therefore undertaken in which estimates of hospitalisation per treatment phase and per 100 patient weeks of treatment were made, one for patients

[redacted]

[redacted]

[redacted]The results when all study countries were considered are summarised in Table 10.

Table 10. Hospitalisation per treatment phase and 100 weeks of treatment

Analysis	Treatment group	Patients with MRU recorded N RATE/100 wks of treatment	All patients at risk (MRU recorded + MRU not recorded) N RATE/100 weeks of treatment
Hospitalisations per progression-free phase	AAP	[redacted]	[redacted]
	PP	[redacted]	[redacted]
Hospitalisations per 100 weeks of treatment	AAP	[redacted]	[redacted]
	PP	[redacted]	[redacted]

The MS presented a KM analyses of time to first hospitalisation and compared this with time to treatment cessation (for those patients hospitalised). This is reproduced in [redacted] (Section 5.2.6) and shows that for both arms, hospitalisation and discontinuation curves follow approximately parallel trajectories with a few weeks delay between hospitalisation and discontinuation. Given these rate results (Table 10) and the KM analysis the manufacturer argues that MRU use is likely to be the same for each trial arm because it precedes progression and all patients eventually progress.

4.2.9 Skeletal related events (SREs)

A skeletal-related event (SRE) was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. The MS stated that "[redacted]". The FDA medical review commented: *".. use of bisphosphonates, … was remarkably different between the pre-study and on-study periods and the percentages of concomitant bisphosphonate use during study was considerably higher than those of disease progression documented in both arms, making it difficult to evaluate any effect of abiraterone acetate on the incidence of skeletal-related event or time to first skeletal-related event in the trial".*[1]

During the clarification process the manufacturer provided information that indicates that the beneficial effect of abiraterone on SREs was unlikely to be confounded by bisphosphonate use since " *.. there was a lower use of bisphosphonates in the AAP arm (approximately 6% lower) compared to placebo"* and because "*…PP subjects were more likely to start bisphosphonates earlier than AAP subjects and were also more likely to require bisphosphonate initiation",* and therefore "*the reduced number of SREs and the delay in SREs observed in the AAP arm compared to PP, is more likely to have been attenuated by the increased use, and earlier use, of bisphosphonates in the PP arm".*

4.2.10 Safety and tolerability

Details of adverse events and other safety data come from the COU-AA-301 trial. The safety population included all patients who were randomised and received any study medication (AAP, n=791 and PP, n=374). Analysis for the OPC population was not undertaken. Details are provided in MS section 5.9 in which both primary (12.8 months median follow-up) and updated analyses (20.2 months median follow-up) were presented. The main features are briefly described below.

Almost all patients in the study reported at least one adverse event. At primary analysis time point, most frequently reported AEs (mostly grade 1 or 2) were fatigue, back pain, arthralgia, bone pain, nausea and constipation. Other commonly reported AEs in AAP arm and PP arm were anaemia (22% vs. 26%), vomiting (21% vs. 25%), [redacted] pain in extremity (17% vs. 20%), diarrhoea (17% vs. 13%), [redacted] asthenia (13% in both groups), dsypnoea (13% vs. 12%), [redacted], urinary tract infection (11% vs. 7%), [redacted] and [redacted]. All these events were primarily grade 1 or 2 events.

The most commonly reported grade 3 or 4 events were fatigue, anaemia, back and bone pain (Table 11). In the updated analysis, the incidence of individual grade 3 or 4 events increased by only 2% relative to the primary analysis.

Table 11. Incidence of frequently reported adverse events at primary endpoint

	All grades			**Grade 3 or 4 events**	
Event, n (%)	**AAP (n=791)**	**PP (n=394)**	**Events, n (%)**	**AAP**	**PP**
Fatigue	346 (44%)	169 (43%)	Fatigue	66 (8%)	39 (10%)
Back pain	233 (30%)	129 (33%)	Anaemia	59 (8%)	29 (7%)
Arthralgia	215 (27%)	89 (23%)	Back pain	47 (6%)	38 (10%)
Nausea	233 (30%)	124 (32%)	Bone pain	44 (6%)	29 (7%)
Constipation	206 (26%)	120 (31%)			
Bone pain	194 (25%)	110 (28%)			

Adverse events related to mineralocorticoid excess were observed more frequently in patients taking abiraterone acetate than those taking placebo (55% vs. 44%). The events were fluid retention and oedema, hypokalaemia, hypertension, cardiac disorders and liver-function test abnormalities. The incidence of fluid retention and oedema was higher in the AAP arm than in the PP arm (31% vs. 22%) however grade 3 or 4 peripheral oedema was low in both groups (2% in AAP vs. 1% in PP). Also, more patients in the AAP arm had hypokalaemia compared to the PP arm (17% vs. 8%) and the incidence of grade 3 or 4 hypokalaemia was higher in the AAP arm (4% vs. 1%). Hypertension occurred in approximately 10% of patients taking AAP compared to 7% taking PP. The incidence of

grade 3 or 4 hypertension was low (1% in AAP arm vs. <1% in PP arm). In the updated analysis, the manufacturer standardised adverse events for duration of treatment exposure and found [redacted]

Cardiovascular related adverse events were more commonly reported in the AAP group compared to the PP group (13% vs. 11%, p=0.14) however these events were primarily grade 1 or 2. The increment in cardiac disorders did not significantly increase fatal cardiac events (1.1% with AAP vs. 1.3% with PP). The cardiac-related deaths were low and similar between the two groups. The most frequently reported cardiac events were tachycardia (3% for AAP vs. 2% for PP, p=0.22) and atrial fibrillation (2% vs. 1% respectively, p=0.29).

The published paper states that the manufacturer needed to amend their protocol and recommend regular liver-function tests in the first 12 weeks, as grade 4 elevations in aminotransferase level were observed early in the trial. The incidence of liver-function test abnormalities was similar between the groups (all grades: 10% for AAP, 8% for PP; grade 3 or 4 changes: 3.5% for AAP and 3.0% for PP). Grade 3 or 4 elevation in AST (aspartate aminotransferase) (1.4% for AAP; 1.6% for PP) and ALT (alanine aminotransferase) (1.0% for AAP; 1.1% for PP) levels were similar between the groups. The grade 4 elevation in aminotransferase level was also similar in the two treatment arms (0.3% for AAP; 0.5% for PP).

The proportion of patients discontinuing treatment because of adverse events was similar between the groups (19% with AA vs. 23% with PP, p=0.09). The occurrence of adverse events leading to dose modification was also similar across the groups (Table 12). Dose modification in both groups occurred for various reasons including: a) adverse events or toxicity, b) serious adverse events, c) hospitalisation, d) restarting the dose. A similar proportion of patients died within 30 days after the last dose of study medication (11% for AAP and 13% for PP), mainly due to disease progression. More patients in the PP arm died due to treatment-emergent adverse events compared to those in the AAP arm (MS 15% vs. 11% or according to the EMA document[17] 14.7% and 11.6%).

Table 12. Number of dose modifications in the trial

	AAP (n=791)	PP (n=394)
Number of abiraterone dose reduction		
0	763 (96.5%)	389 (98.7%)
1	23 (2.9%)	5 (1.3%)
2	5 (0.6%)	0
Number of prednisolone dose reduction		
0	765 (96.7%)	390 (99.0%)
1	26 (3.3%)	4 (1.0%)
2	0	0

The data in the table comes from (supplementary table 3 of the published paper)[20]

Adverse events associated with mitoxantrone treatment of mCRPC patients

Mitoxantrone (or MP) was identified as one of the comparators in the NICE final scope. However the manufacturer was not able to undertake any comparison with AAP because of lack of direct and indirect evidence linking mitoxantrone against abiraterone. The manufacturer also suggested that only 10% of the patient population in the UK are likely to receive mitoxantrone as second-line chemotherapy. The ERG's clinical advisor confirmed this view. The ERG's clinical advisor added that reasons for its minimal use are lack of overall survival (also reported in the MS) and toxicity. Therefore, the ERG looked at the TROPIC study, a phase III trial of cabazitaxel plus prednisolone compared against mitoxantrone plus prednisolone in patients with mCPRC who had failed on or after docetaxel therapy, to provide some information about safety and tolerability of this drug.[31] The most common adverse events reported in the TROPIC study among patients taking mitoxantrone were haematological – leukopenia (92%), neutropenia (88%), anaemia (81%) and thrombocytopenia (43%) (Table 13). The frequently reported non-haematological events were fatigue (27%), nausea (23%) and constipation (15%). The most common grade 3 or 4 haematological events were neutropenia - some febrile cases of neutropenia, leukopenia and anaemia. In approximately 3% of the patients, fatigue and back pain were grade 3 or 4 adverse events. One death in the mitoxantrone arm was associated with neutropenia.

Table 13. Adverse events (all grade or grade 3/4) in patients taking mitoxantrone (TROPIC study)

Mitoxantrone (n=371)			
All grade		**Grade ≥ 3%**	
Leukopenia	92%	Neutropenia	58%
Neutropenia	88%	Febrile neutropenia	1.3%
Febrile neutropenia	-	Leukopenia	42%
Anaemia	81%	Anaemia	5%
Thrombocytopenia	43%	Thrombocytopenia	2%
Fatigue	27%	Fatigue	3%
Nausea	23%	Back pain	3%
Constipation	15%	Pain	2%
Asthenia	12%	Bone pain	2%
Back pain	12%	Pain in extremity	1%
Diarrhoea	11%	Constipation	1%
Vomiting	10%	Arthralgia and UTI	1%

The data in the table comes from the published paper (TROPIC study)[31]

Critique of the safety data

The EMA considers abiraterone to be generally safe;[17] the ERG found no contradictory evidence.

The ERG notes that in the manufacturer's safety and tolerability submissions to the FDA[1] and EMA,[17] a phase I and a phase II trial contributed data in addition to the COU-AA-301 trial. The ERG believes these additional data would have negligible impact on the results presented in the MS to NICE.

The compliance with abiraterone treatment was high. Although all patients reported at least one adverse event, they were generally grade 1 or 2 events. The adverse events were generally manageable and reversible. The adverse events due to mineralocorticoid excess (peripherial odema, fluid retention, hypokalaemia and hypertension) were seen more frequently in patients taking abiraterone however they were generally grade 1 or 2 events. The incidence of grade 3 or 4 toxicities due to mineralocorticoid excess was low and similar across the groups. The EPAR[17] state that if prednisolone is used concurrently with abiraterone from the start of therapy and electrolytes monitored frequently, then the incidence of adverse events due to mineralocorticoid excess reduces, as was seen in the COU-AA-301 trial.

The EPAR mentioned that the mechanism responsible for increase in the incidence of UTI (urinary tract infection) in the AAP arm was unclear.[17] The EMA had some concerns regarding development of cardiac arrhythmias due to chronic androgen deprivation therapy associated with prolong QT interval. However in the COU-AA-006 trial designed specifically to explore this issue, abiraterone did not demonstrate this effect.

It is important to note that abiraterone is not associated with some of the more debilitating toxicities that are often seen with cytotoxic drugs such as mitoxantrone such as myelosuppression, diarrhoea, asthenia, alopecia and others. The drug seems generally safe and the toxicities associated with it are relatively mild in the context of the disease and easily manageable.

4.2.8 Additional clinical work conducted by the ERG

4.2.8.1 Comparators

Mitoxantrone

The MS does not present effectiveness results for mitoxantrone which was identified as one of the comparators in the NICE final scope.

In the economic model, OS under mitoxantrone has been taken to be equal to PP arm of the COU-AA-301 trial. Progression free survival (PFS) is modelled on treatment discontinuation of the PP arm while treatment discontinuation is based on an analysis of the TROPIC study.[31]

TROPIC study: This was an open label randomised phase III trial that compared efficacy and safety of cabazitaxel plus prednisone against mitoxantrone plus prednisone in patients with mCRPC whose disease has progressed during or after docetaxel therapy. The trial was carried out in 146 centres in 26 countries and recruited 755 patients – 377 to mitoxantrone and 378 to cabazitaxel. The baseline characteristics between the two groups were well-balanced. Please see the table below (Table 14).

Table 14. Baseline characteristics of patients in the TROPIC study[31]

	Mitoxantrone (n=377)	**Cabazitaxel (n=378)**
Age, median (years)	67	68
Ethnic origin: White	83%	84%
ECOG status 0 or 1	91%	93%
Metastasis to bone	87%	80%
Metastasis to viscera	25%	25%
Pain at baseline	45%	46%
Previous therapy		
Hormonal	99%	99%
1 chemotherapy regimen	71%	69%
2 chemotherapy regimens	21%	25%
>2 prior chemotherapy regimens	8%	6%
Radiation	59%	61%
Surgery	54%	52%
Biological agent	10%	7%
Number of previous docetaxel regimens		
1	87%	84%
2	11%	14%
>2	2%	2%
Total previous docetaxel dose (mg/m^2)	529.2 (380.9 to 787.2)	576.6 (408.4 to 761.2)
Disease progression relative to docetaxel administration		
During treatment	28%	30%
<3 months from last dose	48%	42%
≥3 months from last dose	24%	27%
Unknown	1%	1%
Median time from last docetaxel dose to disease progression (months)	0.7 (0.0 to 2.9)	0.8 (0.0 to 3.1)

The patients were allowed to take bisphosphonates if they had been taking these at a stable dose for 12 weeks prior to the study. Patients received either cabazitaxel at a dose of 25 kg/m^2 intravenously over 1 hour or mitoxantrone 12 mg/m^2 intravenously over 15 to 30 minutes every 3 weeks. The treatment was given for a maximum of 10 cycles to reduce risk of mitoxantrone related cardiac toxicity. All patients also received oral prednisolone at a dose of 10 mg/day. A single intravenous dose of an antihistamine, corticosteroid and histamine H_2-antagonist was given 30 minutes or more before administering cabazitaxel.

In the absence of direct and indirect evidence Table 15 below compares data reported in the cabazitaxel submission and TROPIC study against PP arm of the COU-AA-301 study.

Table 15. Comparison of mitoxantrone against PP arm

	Mitoxantrone (cabazitaxel submission and TROPIC study)[3,31]	PP arm (COU-AA-301)
Median OS	12.7 months	11.7 months
Treatment discontinuation	-	3.7 months
Composite PFS	1.4 months	-
Median modified PFS	-	[redacted] months*
Tumour progression	5.4 months	-
Time to PSA progression	3.1 months	6.6 months
* read from graph see [redacted]		

Median times for OS were similar. PFS in the cabazitaxel submission was a composite outcome in which progression corresponded to the first event of any of the following: death, tumour progression, PSA progression, pain progression, or symptom deterioration. The median PFS was 1.4 months. The PFS events were made up of: PSA progression (49.3%), death (7.7%), tumour progression (18%), pain progression (18.6%) and symptom deterioration (3.7%).

The definition of Modified PFS (mPFS) used in the abiraterone submission corresponds in some respects only with the criteria for the composite PFS outcome of the cabazitaxel submission (Table 15) and the medians to progression for these differ somewhat (1.4 versus 2.76 months).

The ERG considers that the manufacturer's assumption that OS with mitoxantrone is the same as that of the PP arm of the COU-AA-301 trial is reasonable (11.7 months PP, and 12.7 months for mitoxantrone in the TROPIC trial). The difficulties of estimating progression in mCRPC mean that the assumption that progression on mitoxantrone approximates to treatment discontinuation in the PP arm of COU-AA-301 is associated with considerable uncertainty but may represent a defendable compromise.

Mitoxantrone use as first line therapy

The manufacturer found three studies [34-36] of mitoxantrone used in combination with corticosteroid compared against corticosteroid in chemotherapy naïve patients.

Tannock and colleagues recruited 161 patients with painful hormone-refractory prostate cancer to mitoxantrone + prednisone or prednisone alone.[36] The primary outcome measure of the study was palliative response, defined as a two-point reduction in pain without increment in analgesic use during 2 consecutive evaluations at least 3 weeks apart. It also explored other outcomes such as reduction of ≥50% in use of analgesics without increment in pain, duration of response, survival and health related QoL. The study concluded that there was no difference in overall survival between the two groups. Palliative response was observed in comparatively more patients taking mitoxantrone than those taking prednisolone (29% vs. 12%). The duration of palliation was also longer in those taking mitoxantrone. Most patients responding to treatment had better QoL.

Berry and co-workers conducted a multicentre phase III trial to compare median time to treatment failure with mitoxantrone plus prednisone versus prednisone alone.[34] The trial recruited 120 patients with asymptomatic, hormone refractory, progressive prostate cancer who received either mitoxantrone 12 mg/m^2 intravenously once every 3 weeks for 6 cycles in combination with 10 mg prednisolone per day. The time to treatment failure was a composite endpoints, consisting of time to disease progression, time to toxicity or death, or time to initiation of alternate therapy. The median overall survival in the mitoxantrone group was slightly better compared to the prednisone alone group (23 months vs. 19 months).

Kantoff and colleagues conducted a trial on 248 patients with hormone-refractory prostate cancer to explore if there is an overall survival advantage with mitoxantrone + hydrocortisone (M+H) over hydrocortisone alone (H).[35] There was delay in time to treatment failure and disease progression in the mitoxantrone group compared to cortisone only group but the overall survival between the two was not different (12.3 months for M+H vs. 12.6 for H).

Other potential comparators

The ERG's clinical advisor mentioned that there are currently two innovative drugs with very different mechanisms namely i) PROVENGE and ii) MDV3100. Details in Appendix 4.

The ERG carried out a search for ongoing abiraterone studies. These are listed in Appendix 2.

4.3 Conclusion

Although derived from only a single RCT there is compelling evidence that abiraterone significantly prolongs OS and extends time to progression. The intervention is convenient for the patient and the NHS, in that it is orally self-administered. The side effect profile for abiraterone is of less concern than that of the designated active comparator (mitoxantrone); furthermore, although mitoxantrone may have a palliative effect, there is no convincing evidence that it prolongs survival when used as first or second line therapy in this population. Given these results, the main decision problem hinges on whether the nature and quality of the extended survival experienced by patients treated with abiraterone is worth the extra cost incurred with its use. Therefore, it is evident that estimations of the quality of life for patients in the non-progressed and progressed states under abiraterone, mitoxantrone and BSC therapies are the most critical issues for the decision problem.

The trial only collected HRQoL data, including FACT-P which was used for estimating utility, while patients received treatment. The QoL data evidence is consistent with benefit from abiraterone in terms of delayed deterioration in QoL and superior QoL during treatment with abiraterone than during treatment with placebo. The trial provided no evidence that could be of use in estimating QoL following treatment cessation (i.e. of the progressed state).

5. ECONOMIC EVALUATION

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer carried out a full systematic review to identity relevant cost-effectiveness studies. The ERG believes that the MS systematic review was of good quality. No relevant studies were identified. There were a few minor criticisms of the search strategy, details of which are given in Appendix 5.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist (TABLE ONLY)

Please see the table below (Table 16).

Table 16. Comparison with NICE reference case

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes. The NICE scope specifies mitoxantrone in combination with prednisolone and best supportive care, which may include corticosteroids. The primary comparison undertaken by the manufacturer is with prednisolone as per the pivotal trial. An additional comparison is undertaken with mitoxantrone in combination with prednisolone.
Patient group	As per NICE scope	Yes. The manufacturer restricted the trial population to those having had experience of at least one prior chemotherapy.
Perspective costs	NHS and Personal Social Services (PSS)	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost-utility
Time horizon	Sufficient to capture differences in costs and outcomes	10 years which given the patient group and simulated overall survivals is close to lifetime.
Synthesis of evidence on outcomes	Systematic review	The main comparison with prednisolone relies upon the pivotal head to head trial. For the comparison with mitoxantrone in combination with prednisolone the base case assumes progression free and overall survival are as for prednisolone. This appears reasonable for overall survival but may be less reasonable for progression free survival. There is no systematic review or network meta-analysis for the comparison with mitoxantrone.
Outcome measure	Quality adjusted life years (QALYs)	Yes.
Health states for QALY	Described using a standardised and validated instrument	No. FACT-P data were collected during the pivotal trial. FACT-P data were mapped on to EQ-5D utility values from the separate Adelphi database by the manufacturer. The resulting mapping function was used to transform trial based FACT-P values into utilities. A regression analysis was then undertaken to determine the impact of treatment upon this, abiraterone being estimated to yield a [redacted] HRQoL gain over the baseline prednisolone utility of [redacted] for those remaining on treatment. The utility value for survival with progression, and as a consequence the utility decrement for moving into survival with progression, was taken from a paper within the literature.
Benefit valuation	Time-trade off or standard gamble	The EQ-5D utilities for the mapping exercise were derived from the standard TTO reference.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of sensitivity analyses were undertaken.

5.2.2 Model structure

The model structure is relatively straightforward and transparently implemented. The model assumes a three weekly cycle in order to be in line with the MP dosing schedule, and a ten year horizon which is in effect a lifetime horizon. The OS and PFS curves are modelled. The residual is survival with progression. Costs and HRQoL values are attached to these to estimate the overall cost effectiveness of AAP.

For the probabilistic modelling, costs and utilities are treated probabilistically as also are the base case KM curves. This is achieved by simulating a normal distribution around each point of the KM curve based upon that point's standard error estimate. The simulated KM curve remains smooth due to one random variable [0,1] used for each iteration to simulate one KM curve. Each KM curve draws on a different single random variable [0,1].

5.2.3 Population

In the light of the license, the manufacturer concentrates upon a sub-group of the patient population of the pivotal trial, the 1-prior chemotherapy updated analysis. The ERG views this as being the appropriate focus.

5.2.4 Interventions and comparators

A pivotal trial (COU-AA-301) is included where in abiraterone acetate plus prednisolone (AAP) is compared to placebo plus prednisolone (PP).

An additional comparison is made with mitoxantrone (with or without prednisolone, M or MP) according to the NICE scope. Both the manufacturer and the ERG view this as secondary.

5.2.5 Perspective, time horizon and discounting

The perspective is that of the patient for benefits and the NHS and PSS for costs. A lifetime horizon is adopted, with the base case discounting costs and benefits at 3.5%.

5.2.6 Treatment effectiveness and extrapolation

The base case applies the Kaplan Meier OS curves from the pivotal trial up to the point where only 10% remain at risk. The manufacturer justifies this due to censoring at the end of the trial period

making the tails of the Kaplan Meier curves less reliable. Note that due to the 2:1 randomisation within the pivotal trial, at cut-off the absolute numbers at risk within the AAP arm are roughly double that of the PP arm. Thereafter the overall survival curves are extrapolated using a constant hazard, this being estimated from the baseline to cut-off at time t with survival S(t) as . Note that the model has the facility to use a Weibull for this extrapolation, and the facility to model the entire overall survival curve using a Weibull.

Since progression is apparently often being formally assessed or recorded, treatment discontinuation is taken as a proxy for progression. For the AAP arm a similar approach to the modelling of overall survival is applied. The base case applies the Kaplan Meier survival on treatment curves from the pivotal trial up to the point where only 5% remain at risk. The manufacturer justifies this lower cut-off for survival on treatment since there is less censoring than within the overall survival curves. Thereafter the AAP survival on treatment curve is extrapolated using a constant hazard. For the PP arm, since the Kaplan Meier curve for survival on treatment is, or is virtually[b], complete this is used without any extrapolation.

The extent to which survival on treatment is synonymous with progression free survival is a moot point. It may be the best data that is available. But it can be noted that within the presentation on unplanned resource use, the manufacturer presents Kaplan Meier curves for hospitalisation rates alongside the Kaplan Meier curves for survival on treatment ( ).

Table 17. Hospitalisation rates and patients remaining on treatment

	Mean time to event (wks)			Median time to event (wks)		
	1st hosp.	TX duration	net	1st hosp.	TX duration	net

The ERG's clinical expert points out that one of the main indicators of progression is hospitalisation. The above may suggest that treatment duration may not be synonymous with progression free survival (Table 17). But to some extent the distinction may be relatively unimportant for the comparison of AAP with PP within the economic model. If resource use and HRQoL data also apply the same

[b] Within the electronic model for the 1-prior chemotherapy PFS KM data, it appears that a little over 2% have not discontinued at the end of the KM data. While relatively minor, retaining this and extrapolating using the constant hazard derived from the entire KM curve increases the average undiscounted time spent in the PP and the MP arms by around 2% from years to years. The impact upon the ICER is minor, increasing the PAS inclusive cost effectiveness of AAP relative to PP from per QALY to per QALY, and from per QALY to per QALY when compared to MP.

definitions, the analyses would be aligned. But discrepancies may arise if data collection points are skewed and do not reliably capture data over the relevant periods, however defined. Problems may also arise if data are drawn from other disparate sources and applied to periods within the model.

5.2.7 Mitoxantrone treatment in the model

The base case assumes that PFS and OS curves for PP also apply for MP. The main distinction for MP compared to PP are that: (i) treatment costs differ (treatment lasts a maximum of ten cycles), (ii) there is a HRQoL loss and an increased cost due to more adverse events from MP treatment (this is applied while on MP treatment), (iii) cessation of treatment is not synonymous with progression, (iv) PFS is drawn from the PP arm; (v) there is a HRQoL gain from reduced pain and (vi)other symptoms are taken to be equal to that for AAP PFS.

Proportion of patients on mitoxantrone treatment

Patients remain on treatment within the mitoxantrone arm for a maximum of 10 cycles, but are assumed to follow the prednisolone PFS curve as shown below (Figure 8).

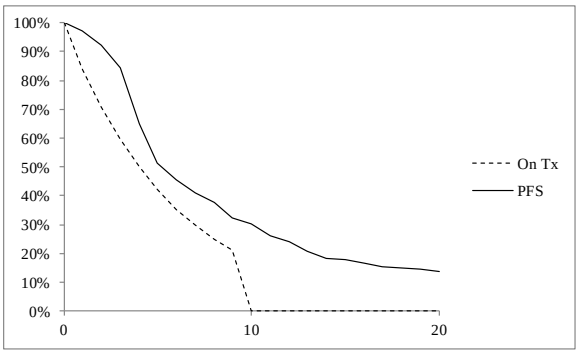


Figure 4. Mitoxantrone on treatment and progression free survival

As drawn from the electronic copy of the manufacturer model, the proportion of patients remaining on mitoxantrone is modelled using the exponential where t is the time in years. This is up to a maximum duration of 10 mitoxantrone 3 weekly cycles, as in the TROPIC trial reported by de Bono and colleagues.[31] This results in the following proportion of mitoxantrone patients remaining on treatment (Table 18).

Table 18. Proportion of mitoxantrone patients remaining on treatment

Cycle	Years	MP Tx
0	0.000	100%
1	0.057	84%
2	0.115	71%
3	0.172	59%
4	0.230	50%
5	0.287	42%
6	0.345	35%
7	0.402	30%
8	0.460	25%
9	0.517	21%
10	0.575	0%

5.2.8 Health related quality of life

HRQoL while on AAP or PP treatment and progression free

Neither the EQ-5D nor SF-36 were collected during the pivotal trial (COU-AA-301) and as a consequence the manufacturer has undertaken a two stage analysis of FACT-P data.

- Stage I: Data from the separate Adelphi database which contains EQ-5D and FACT-P data for mCRPC patients is used to derive a mapping function from FACT-P to utility values through OLS regression.
- Stage II: The FACT-P data from patients on treatment within the pivotal trial are converted to utilities, and regression analysis applied to derive a treatment effect.

The construction of the mapping function broadly mirrors that of Wu and colleagues.[37] As stated by the manufacturer and verified by the ERG, the mapping function reported by Wu and colleagues does not generate sensible results when applied to FACT-P data with utility values greater than 1 occurring. The EQ-5D data set is not specific to UK patients, but is converted to utility values using the UK EQ-5D social tariff. It should be noted that while some baseline characteristics are quite similar between the Adelphi data set and the pivotal trial, the majority of patients in the Adelphi data set [redacted] compared to the average FACT-P of 106.3 in the pivotal trial (See Table 19).

Table 19. Adelphi patient group compared to the pivotal trial

	Adelphi (n=291)	Trial 301 (n=1195)
Age	[redacted]	69.2
BMI	[redacted]	27.5
Ethnicity White Black Hispanic/Spanish Other	[redacted]	 93% 4% 3%
Performance status	[redacted]	90% were ECOG 0-1
Chemotherapy status No chemotherapy Current chemotherapy Prior Chemotherapy	[redacted]	 0% 0% 100%
Distant metastasis Node Bone Other	[redacted]	 44% 90% Unknown
Mean FACT-P	[redacted]	106.3

In response to ERG clarification question B7 and an accompanying supplied reference, the average UK HRQoL was [redacted] within the Adelphi data set. The reference is not sufficiently detailed to be able to state the following with certainty, but it appears that across all patients, when the EQ-5D values were valued using the UK EQ-5D tariff, within the Adelphi dataset the average value for those

not receiving chemotherapy was [redacted], while the value for those receiving chemotherapy was slightly lower at around [redacted].

This results in the following mapping function for FACT-P to utility, which has an R^2 of 0.385 ([redacted]).

[redacted]20[redacted]

	Coef.	p-value
[redacted]	[redacted]	[redacted]

To derive the treatment arm effect, the individual patient changes from baseline utility as implied by the FACT-P mapping function are calculated and regressed on the baseline utility with a dummy variable for the AAP treatment arm. All parameters [redacted] (Table 21).

Table 21. Manufacturer multivariate utility models: change from baseline utility coefficients

	All patients	1 prior
Intercept Treatment group: AAP vs. PP Baseline Utility Score	[redacted]	[redacted]

Note that there is no explicit modelling of adverse events within the treatment model, the assumption is that any differences between the treatment arms in adverse events while on treatment are reflected in the treatment group coefficient. Certainly serious adverse events (SAEs), as summarised in Table 22 of the submission, appear to be reasonably well balanced between the arms of the trial, with the exception of nervous system disorders where a statistically significant protective effect from AAP over PP is reported. This arises from reduced rates of spinal cord compression which is statistically significant in the primary analysis across all patients, but marginally fails to be so in the updated analysis[c] where it occurs in 2.9% of patients in the AAP arm compared to 5.1% of patients in the PP arm. For these patients, spinal cord compression may have quite a large impact on FACT-P scores and the resulting utility estimates.

As outlined in greater detail in the ERG review of the model implementation, rates of reporting vary considerably between cycles and the average values between cycles change quite considerably, particularly within the PP data. A literal reading of Appendix 15 allows for the possibility that cycle number may be statistically significant.

[c] It is unclear whether the utility analysis used the primary or the updated analysis.

On the basis of this, the manufacturer applies the average baseline utility of [redacted] for patients on treatment in the PP arm for the 1-prior chemotherapy group. A utility increment of [redacted] is added for the AAP arm to yield a utility for patients on treatment of [redacted].

SAEs are not included in the regression for estimating the on-treatment effect. But a separate, parallel regression is used to estimate an average utility decrement for SAEs of [redacted] for the 1-prior chemotherapy group. This is only used to condition the MP on treatment utility. The base case assumes the same palliative effect as abiraterone, so adds [redacted] to [redacted]. But it nets out the average SAEs reported for abiraterone and mitoxantrone to arrive at an estimated net increase of 32% in SAEs from mitoxantrone use. This yields an on-treatment decrement of 32% * [redacted] = [redacted] for MP.

HRQoL subsequent to progression free survival

FACT-P values were reported among a subset of patients at end of treatment. Applying the manufacturer's mapping function to these, suggests end of treatment utilities of [redacted] for the AAP arm and [redacted] for the PP arm. But the manufacturer notes that the number of patients reporting FACT-P was small, around 107 patients in the AAP arm and 62 patients in the PP arm.

For this reason the manufacturer selects a representative value from Sandblom and colleagues[2] of 0.500, this being a rough average of the values reported for the final 8 months of life. The manufacturer base case estimates an average duration of survival with progression of 9.9 months for AAP and 11.0 months for PP.

HRQoL summary

The above yields the following HRQoL values for the manufacturer base case (Table 22).

Table 22. HRQoL values used within the manufacturer model

	AAP	PP	MP on TX	MP off TX	Progressed
Baseline On Tx direct On Tx AEs	[redacted]	[redacted]	[redacted]	[redacted]	0.500
Value	[redacted]	[redacted]	[redacted]	[redacted]	0.500
increment vs PP increment vs Prog.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As summarised in the above, there is a [redacted] utility increment from AAP over PP. The ERG views it as reasonable for an increment to apply, given the differences in patients outcomes while on treatment. These estimates are from the same source and so are directly comparable.

There is a large utility increment from remaining progression free compared to surviving with progression. As reviewed later, in comparison to other assessments this step change may be quite large. The data which give rise to this step change are from two entirely separate sources, which increases the uncertainty around the reasonableness of the estimate.

5.2.9 Resources and costs

Direct drug costs, administration and monitoring costs

Abiraterone 4 weekly packs at a cost of [redacted] are assumed to be divisible into 3 weekly packs at a cost of [redacted], in order to be in line with the model cycle duration. Note that the manufacturer model applies half cycle correction to the direct drug costs; e.g. for the first cycle of the model rather than 100% of the 3 weekly cost of abiraterone being incurred an average of 98.7% is assumed.

Prednisolone is dosed at 10mg, the cost of which is negligible.

Mitoxantrone dosing is 12mg per m^2, which given an average surface area of 2.01m^2 is assumed to require two 20mg vials per dose at a cost of £200. The administration cost for this is taken as an outpatient appointment code SB12Z – deliver simple parenteral chemotherapy at first attendance at a cost of £248. This £248 is in addition to the resource use tabulated below.

Additional drug costs are included for the 37% of patients receiving bisphosphonates within the trial. No additional administration cost was included for this, which may not be reasonable given that zoledronic acid is an IV infusion and might increase these costs by 25% to 50%.

Administration and monitoring costs are based on the following resource use, costed using NHS reference cost and PSSRU sources (Table 23).

Table 23. On treatment schedule of routine visits

	OP visit	Frequency	Cost/mth
Mitoxantrone on tx	Chemo specific OP appointment + FBC, PSA and liver & kidney function tests	3 weekly	£300
Abiraterone months 1-3	Alternates between consultant oncologist and nurse specialist + FBC, PSA and liver & kidney function tests	2 weekly	£279
Abiraterone months 4+	Alternates between consultant oncologist and nurse specialist + FBC, PSA and liver & kidney function tests*	4 weekly	£150
Prednisolone	Alternates between consultant oncologist and nurse specialist + FBC, PSA and liver & kidney function tests	6 weekly	£114
Mitoxantrone off tx but PFS	Alternates between consultant oncologist and nurse specialist + FBC, PSA and liver & kidney function tests	6 weekly	£114
Off tx with progression	Alternates between consultant oncologist and community nurse + FBC and liver & kidney function tests	6 weekly	£146
*Tests at the same average rate per week as for prednisolone. Costs inclusive of CT scans, MRI scans, ultrasound and bone scans			

The manufacturer also assumes around 3% of patients each month would require a CT scan, a radiographic MRI scan, ultrasound or a bone scan.

ERG expert opinion suggests that the above resource use is generally reasonable, and that two appointments would be necessary for those on mitoxantrone treatment: one for OP administration and one consultant led OP review every 3 week cycle.

Adverse event costs

The net costs of adverse events are only applied for those on mitoxantrone treatment, all other costs being assumed to have been captured within the unplanned medical resource use outlined below. The proportion of patients remaining on mitoxantrone treatment are coupled with the units costs of adverse events as estimated by the manufacturer to yield an additional average total adverse event net cost for mitoxantrone of £381 over abiraterone[d]. (Table 24)

[d] Note that there is a per cycle reduction in adverse event costs of £0.89 applied from cycle 2 for those remaining on mitoxantrone. This has not been reviewed by the ERG and will not affect results.

Table 24. Additional adverse event costs from mitoxantrone over abiraterone

	AAP	MP	net	Unit cost	Net cost
Neuropathy	0%	1%	1%	£846	£5
Neutropaenia	0%	58%	58%	£865	£501
Febrile Neutropaenia	0%	1%	1%	£4,564	£28
Thrombocytopaenia	1%	2%	1%	£748	£5
Anaemia	8%	5%	-3%	£1,183	-£34
Oedema (Peripheral)	2%	0%	-2%	£914	-£16
Hypokalaemia	4%	0%	-4%	£982	-£43
Hypertension	1%	0%	-1%	£364	-£5
Arthralgia	5%	1%	-4%	£271	-£11
Asthenia	3%	2%	-1%	£12	£0
Diarrhoea	1%	0%	-1%	£1,015	-£9
Dyspnea	2%	1%	-1%	£0	£0
Fatigue	9%	3%	-6%	£12	-£1
Nausea	2%	0%	-2%	£550	-£10
Vomiting	3%	0%	-3%	£1,097	-£29
Total	43%	74%	32%		£381

Unplanned resource use during progression free survival

Unplanned resource use was drawn from data collected within the trial and as summarised within Appendix 16 of the submission.

The ERG clarification question B5 asked for clarification of this resource use and a disaggregate presentation of the data underlying the estimates of resource use up to progression. Additional details of the MRU data of those who had yet to progress at end of trial would also have been useful at the clarification stage. Regardless of this, despite its absence being drawn to the attention of NICE, the manufacturer has not supplied the relevant file[e].

In the absence of any further data, the ERG has had to rely upon Appendix 16 and expert opinion. Appendix 16 of the submission outlines that unplanned medical resource use was collected within the pivotal trial. The resource use collected provided for a number of categories such as GP visits and nurse visits, with a free text catchall category, but the bulk of the unplanned resource use identified related to hospitalisations.

In the light of this, the manufacturer presented an analysis of the time to first hospitalisation across the ITT population, as shown in the Kaplan Meier curves of [redacted] and Table 17 above. Across all patients in all countries, and the subset of UK patients, the rate of hospitalisation as summarised in Table 78[f] of the submission was as below (Table 25 and Table 26).

[e] NICE_Response_Hospitalisations and Other Costs_MRU Analysis Tables 81 and 82.rtf
[f] This gives N as 672 for the AAP arm and 380 for the PP arm, as compared to a recruitment of 797 and 398.

Table 25. Hospitalisation rates per 100 patient weeks: All patients

		All patients				Patients with MRU record			
		N	ICU	Non-ICU	All	N	ICU	Non-ICU	All
All	AAP	[redacted]							
All	PP								
UK	AAP								
UK	PP								

Table 26. Hospitalisation rates per 100 patient week on treatments: All patients

		All patients				Patients with MRU record			
		N	ICU	Non-ICU	All	N	ICU	Non-ICU	All
All	AAP	[redacted]							
All	PP								
UK	AAP								
UK	PP								

The Kaplan Meier curves presented in Table 17 and [redacted] suggest that hospitalisations occur close to progression. In the light of this the manufacturer further analysed resource use data restricted to those patients who had ceased treatment (The data were further restricted to those with a recorded non-zero medical resource use on the assumption that progression would incur some unplanned resource use. Any zero medical resource use record among those having ceased treatment or progressed was consequently assumed to be a recording error).

The resulting restricted UK data set was based upon a UK AAP sample size of 126 patients, of whom 16 were excluded due to remaining on treatment and a further 24 because their recorded medical resource use was zero. The UK PP sample size of 68 patients had all ceased treatment, with 13 being excluded because their recorded medical resource use was zero. Within this UK sample, a similar percentage of 22% of AAP patients and 19% of PP patients were excluded due to having no unplanned medical resource use recorded. This gave sample sized of 86 and 55. It is unclear why the previous hospitalisation rates suggest a sample size of only 50 for the UK PP arm. This resource use was then apparently costed using standard UK sources.

GLM regression analysis was then used to explore the sensitivity of this resource use to treatment arm and treatment duration as below (Table 27).

Table 27. GLM regression for PFS medical resource use

	DF	Estimate	s.e.	Wald X^2	Pr > Wald X^2
Intercept	1	[redacted]			
AAP arm dummy	1				
Treatment duration	1				
Scale	1				

Table 28. Average MRU per week: UK patients

	N	GP	RN	Oncologist	Hosp	Other	Total
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29. Total progression free MRU : UK patients

	N	GP	RN	Oncologist	Hosp	Other	Total
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given the similarity of the average cost per week and the average total cost per progression free period for AAP and PP, this would appear to suggest a similar duration of progression free survival among those with non-zero medical resource use records prior to progressing. The average weekly cost for each element within Table 28 is very nearly constant at between 3.57% and 3.67% of the corresponding entry within Table 29. The patients who progressed with non-zero medical resource use records may not be representative of the wider patient group. If so, this could explain the insignificance of the treatment duration parameter within the GLM regression.

The vast majority of the resource use is due to hospitalisation. In the light of the Kaplan Meier curves, the manufacturer assumed a fixed cost for unplanned medical resource use whilst progression free of [redacted]. ERG expert opinion agrees that the bulk of unplanned medical resource use during the progression free period will be concentrated at the end of this period. Whether it is reasonable to treat it as a fixed cost is perhaps more debatable. Given this handling of unplanned medical resource use in the progression free period, it has no impact upon the net outcomes of the modelling.

Resource use subsequent to progression free survival

An additional £262 per cycle is added to the costs of survival with progression. The submission references Appendix 16 and the MRU costing exercise for this. But Appendix 16 does not mention or itemise any post progression costs. It appears that the manufacturer has assumed an arbitrary weekly cost of £87, with no justification for this being presented. The post progression duration dependent costs have some impact upon results. But as the manufacturer base case models the average time spent surviving with progression as being similar between the arms: [redacted] undiscounted years for AAP compared to [redacted] undiscounted years for PP and MP, these are not as large as might initially be anticipated. As a consequence the overall impact of these costs upon total net costs is a saving from AAP of £452 compared to both PP and MP.

It is also assumed that all patients will be prescribed ongoing bisphosphonates at a cost per cycle of £148. ERG expert opinion suggests this is too high, and it may have been more reasonable to assume the same proportion continue on bisphosphonate use as before.

A common [redacted] of patients moving off treatment and into survival with progression are assumed to receive chemotherapy based upon the clinical trial. This is assumed to be cabazitaxel, which when weighted by the [redacted] yields at an average cost of [redacted]. Terminal care costs of [redacted] are broadly common to all arms. While substantial at face value, these costs only result in a small difference in net costs between AAP and PP, and between AAP and MP, of [redacted]. There are some arguments for excluding terminal care cost altogether in order not to skew the results of sensitivity analyses that restrict the model time horizon.

5.2.10 Cost effectiveness results

Manufacturer's base case deterministic results

The manufacturer's base case results in the following disaggregate outcomes with the PAS (Table 30).

Table 30. Manufacturer base case deterministic results: 1 prior chemo

	APP	PP	MITOX
Undiscounted survival years AAP net	[redacted]	[redacted]	[redacted]
Undiscounted PFS years AAP net	[redacted]	[redacted]	[redacted]
Costs			
Direct drug cost Concomitant drug cost Other costs Terminal care costs	[redacted]	[redacted]	[redacted]
Total AAP net	[redacted]	[redacted]	[redacted]
QALYs AAP net	[redacted]	[redacted]	[redacted]

These imply the following cost effectiveness with the PAS (Table 31).

Table 31. Manufacturer base case deterministic cost effectiveness estimates: 1 prior chemo

	Cost	net	QALYs	net	ICER
PP	[redacted]		[redacted]		
MITOX	[redacted]	[redacted]	[redacted]	[redacted]	ext. dominated
AAP	[redacted]	[redacted]	[redacted]	[redacted]	£52,851

Mitoxantrone plus prednisolone is estimated to be extended dominated by abiraterone acetate plus prednisolone, as its cost effectiveness relative to placebo plus prednisolone is estimated as £170,550 per QALY.

For completeness the base case cost effectiveness results for the ITT patient population is £60,292/QALY for AAP versus PP while mitoxantrone (with or without prednisolone) is estimated to be extendedly dominated by AAP (Table 32).

Table 32. Manufacturer base case deterministic cost effectiveness estimates: All patients

	Cost	net	QALYs	net	ICER
PP	[redacted]		[redacted]		
MITOX	[redacted]	[redacted]	[redacted]	[redacted]	ext. dominated.
AAP	[redacted]	[redacted]	[redacted]	[redacted]	£60,292

Manufacturer base case probabilistic results

The central estimates for the base case probabilistic results are similar to those of the deterministic modelling (Table 33).

Table 33. Manufacturer base case probabilistic cost effectiveness central estimates: 1 prior chemo

	Cost	net	QALYs	net	ICER
PP	[redacted]		[redacted]		
MITOX	[redacted]	[redacted]	[redacted]	[redacted]	ext. dominated
AAP	[redacted]	[redacted]	[redacted]	[redacted]	£52,714

Note that despite much in the model being probabilistic, the progression free survival for mitoxantrone is assumed to be the same as for prednisolone. The duration of treatment with mitoxantrone is treated deterministically, and some costs specific to mitoxantrone are treated probabilistically and differ from those of prednisolone. In the light of this it is surprising that the average net cost of mitoxantrone compared to prednisolone is the same as in the deterministic analysis, though the totals actually differ by about 60 pence. This occurs despite the net cost for each iteration within the probabilistic analysis being different from the mean value. The ERG has not traced any logical flaw within the probabilistic modelling to account for this, and it may simply reflect the model being unusually linear for this outcome.

The associated CEAF suggests some uncertainty in the range £40,000 per QALY to £70,000 per QALY. But prednisolone is estimated as clearly being the most cost effective up to £40,000 per QALY and abiraterone as clearly being the most cost effective beyond £70,000 per QALY (Figure 9 and Table 34).

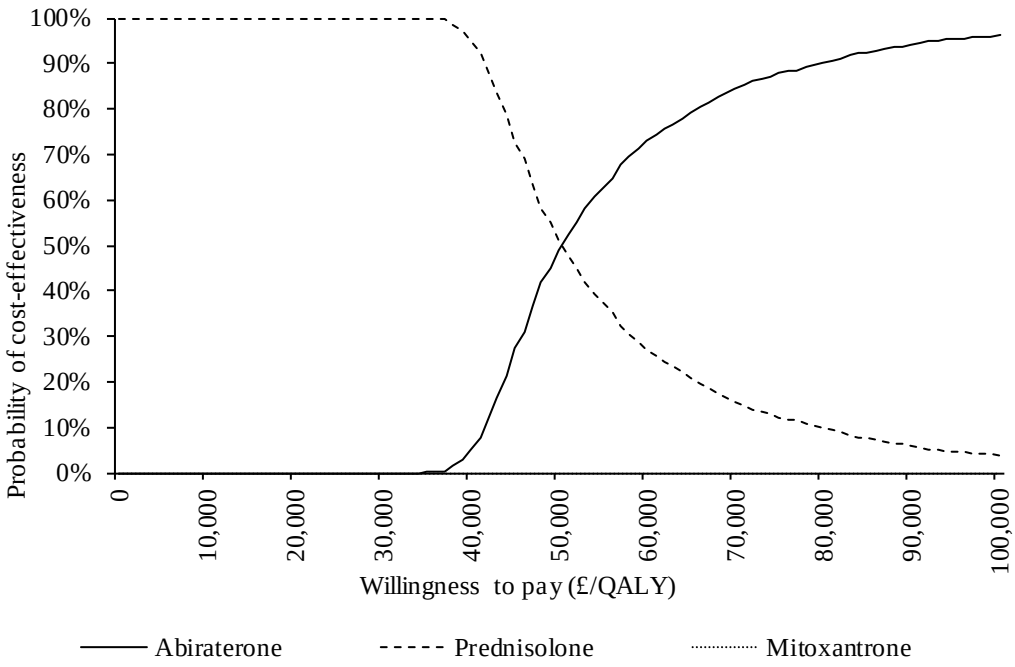


Figure 5. Manufacturer base case CEAFs

Table 34. Probability of cost effectiveness for different willingness to pay values

WTP/QALY	AAP	PP	MITOX
£0	0%	100%	0%
£20,000	0%	100%	0%
£30,000	0%	100%	0%
£40,000	5%	95%	0%
£50,000	49%	52%	0%
£60,000	73%	27%	0%
£70,000	85%	15%	0%
£100,000	97%	3%	0%

5.2.11 Sensitivity analyses

The manufacturer undertook a range of univariate sensitivity analyses (Table 35).

Table 35. Manufacturer univariate sensitivity analyses

		PP	MP
Base Case		£52,851	£46,617
Time Horizon	4 years	£57,057	£50,146
	6 years	£54,066	£47,646
	8 years	£53,141	£46,863
Discount rate - costs	0	£55,309	£49,142
	0.06	£51,279	£45,005
Discount rate - benefits	0	£49,164	£43,252
	0.06	£55,461	£49,006
Overall survival approach	KM+10% cut-off+Weibull projection	£56,484	£49,817
	KM+5% cut-off+constant hazard projection	£54,195	£47,796
	KM+5% cut-off+Weibull projection	£57,298	£50,537
	Parametric (Weibull-placebo, Weibull-AA)	£56,339	£49,691
	Lower end of the 95% CI of KM	£50,679	£44,516
	Higher end of the 95% CI of KM	£55,438	£48,886
PFS approach	KM+5% cut-off+Weibull projection	£53,301	£46,878
	KM+10% cut-off+constant hazard projection	£53,091	£46,755
Median Tx - mitoxantrone	2 cycles	-	£50,128
	7 cycles	-	£43,849
Baseline utility of mCRPC	0.538 (Collins, 2007)[38]	£77,040	£69,640
	0.85 (Krahn, 2003)[39]	£48,451	£42,548
Utility increment abiraterone	[redacted] (-20%)	£54,353	£48,014
	[redacted] (+20%)	£51,708	£45,556
Utility mCRPC in progression	0.40 (-20%)	£51,421	£45,290
	0.60 (+20%)	£54,364	£48,024
	0.46 (Sandblom 2004)[2]	£52,270	£46,077
	0.70	£55,965	£49,518
Utility Grade 3/4 AEs	[redacted]	-	£45,983
Scheduled follow-up costs	-50%	£51,147	£45,699
	+50%	£54,555	£47,534
Unplanned MRU cost	-50%	£53,486	£47,285
	+50%	£52,217	£45,948
Subsequent treatment costs	no cabazitaxel	£52,930	£46,700
GCSF use	no GCSF use	£52,758	£46,541
Bisphosphonate use	50% in PFS and progression	£53,347	£47,139
Adverse event costs - all	-50%	-	£47,179
	+50%	-	£46,054
Terminal care costs	None	£52,960	£46,731
	+20%	£52,829	£46,594

An additional scenario analysis which assumed that MP conferred a PFS advantage over PP, based upon hazard ratios of 0.77 as drawn from Kantoff and colleagues[35] resulted in mitoxantrone being estimated as no longer being extendedly dominated but having a cost effectiveness compared to PP of £21,038 per QALY. Within this analysis the cost effectiveness of AAP compared to MP was estimated as £62,843 per QALY.

Without the PAS, the base case cost effectiveness for AAP compared to PP was estimated as [redacted] per QALY.

5.2.12 Model validation and face validity check

No validation was formally presented, but the OS and PFS curves assumed for the base case are virtually the entirety of the model structure.

5.3 ERG cross checks and critique

Base case results

Re-running the model, the base case deterministic and probabilistic results cross check with those of the manufacturer.

Data Inputs

Correspondence between written submission and sources cited

- Duration and cost of mitoxantrone therapy

The TROPIC trial[31] of cabazitaxel versus mitoxantrone reports a median number of 3 weekly treatment cycles of 4, with only 12% of patients completing the full 10 cycles. The manufacturer estimated an exponential function based upon a median of 5 cycles, though this is complicated by the application of half cycle correction to treatment costs within the manufacturer model. The 4 cycle median as reported by de Bono and colleagues would result in the exponential

which in turn results in a proportion receiving 10 cycles of 12.5% which is in line with that reported in de Bono and colleagues.

It should also be noted that the TROPIC trial had a maximum of 10 cycles for mitoxantrone. This may have resulted in a longer treatment duration than in those trials comparing mitoxantrone with prednisolone, which might be the more natural default. For instance, Berry and colleagues[34] treated up to a maximum of 6 cycles of mitoxantrone. However, ERG expert opinion suggests that 10 cycles is reasonable.

The ERG cannot find the average body area 2.02m^2 for mitoxantrone within the de Bono and colleagues reference,[31] but it does tally with the 2.01m^2 for mitoxantrone reported within the cabazitaxel STA.[3] As an average it implies an average requirement for 24.2mg and two 20mg vials which the manufacturer costs at £200. But this does not take into account the variability in patient

body area and the standard deviation of 0.21m^2. The cabazitaxel STA costs this at an average £187 per patient as compared to the average £200 assumed by the manufacturer.

For the administration cost of mitoxantrone the manufacturer applies the cost for an outpatient HRG SB12Z – deliver simple parenteral chemotherapy at first attendance at a cost of £248. Subsequent administrations are also costed at this amount. The outpatient HRG code SB15Z – deliver subsequent elements of a chemotherapy cycle has a slightly lower outpatient reference cost of £212.

The rates of grade 3 or worse adverse events assumed for mitoxantrone cross check with those reported by de Bono and colleagues.[31] This is with the exception of the assumed 0.8% for neuropathy which the ERG has not been able to source.

- Laboratory test costs

The ERG has been unable to source the £9.03 for a liver function test or the £12.90 for a kidney function test under the stated HRG code DAP841. The same DAP841 – Biochemistry Direct Access: Pathology Services code is applied for a PSA test with the £1.29 cross checking with the 2009-10 reference costs.

Correspondence between written submission and electronic model

The values within the submission and the electronic copy of the model cross check, with the following exceptions:

Table 26 states median duration for mitoxantrone of 12 weeks or 4 cycles, when it appears that the model applies a median of 15 weeks or 5 cycles, albeit with half cycle correction.

<u>Model structure and implementation</u>

- The modelling of overall survival curves and progression free survival curves

In response to the ERG clarification questions A9 the manufacturer supplied the parametric functions estimated for OS in the AAP and the PP arms (Table 36). These appear to be based on KM data to 10% and 5% at risk for OS and treatment discontinuation respectively.

Table 36. Updated analysis 1 prior chemo OS parametric forms

	Intercept	s.e.	Scale	s.e.	Shape	s.e.	AIC	BIC
AAP								
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP								
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These parametric fits were available to the manufacturer for sensitivity analyses.

From this the Weibull appears the best fit for modelling OS for the AAP arm, but the log normal appears to be a better fit for modelling OS in the PP arm as can be seen below over the first 37 cycles or 2 years 2 months of the model ([redacted]). Note that from cycle 29 the number at risk (PP) declines to less than 10%, while from cycle 32 the number at risk declines to less than 5%. Note that in contrast to the constant hazard extrapolation the Weibull fit imposes monotonically increasing hazard beyond the observed data so that abiraterone ceases to deliver survival gain relative to placebo beyond 5.47 years (Appendix 7), whereas with the constant hazard model abiraterone continues to deliver survival gain relative to placebo for up to 10 years.

Although results were not reported in the MS the manufacturer's model retains the facility to apply the log-normal curve for modelling OS in the PP arm, while retaining the Weibull curve for modelling OS in the AAP arm[g]. A problem arises due to the longer tail of the PP log-normal curve crossing over the Weibull AAP arm at cycle 49 of the model at around 2 years 9 months when around 15% of patients are estimated to still survive. From this point onwards, the manufacturer model assumes that both arms follow the AAP Weibull OS curve as illustrated below ([redacted]).

In response to the ERG clarification questions A10 the manufacturer has supplied the parametric functions estimated for PFS in the AAP and the PP arms (Table 37).

[g] Implemented by setting E12 of the *Settings* worksheet to Log-Normal

Table 37. Updated analysis 1 prior chemo PFS parametric forms

	Intercept	s.e.	Scale	s.e.	Shape	s.e.	AIC	BIC
AAP								
Weibull								
Log-normal								
Log-logistic								
Exponential								
Gompertz								
Generalized gamma								
PP								
Weibull								
Log-normal								
Log-logistic								
Exponential								
Gompertz								
Generalized gamma								

For PFS the log-logistic form appears to be the best fit for both the AAP arm and the PP arm. As expected, log-log and log-normal distributions provide similar curves and IC scores. According to AIC and BIC for the AAP arm, Weibull is the best fit after the logarithmic distributions. Again, a problem with cross over occurs when fitting the log-logistic PFS curve for the AAP arm within the context of Weibull OS curve for the AAP arm, in that cross over occurs at cycle 64. For this to be used within the modelling requires a parallel assumption to the manufacturer model assumption for OS, in that when cross over occurs the PFS curve has to be assumed to follow the OS curve ( ).

A key question within the modelling is whether it is most reasonable to apply the Weibull extrapolation for OS in the PP arm, or the truncated lognormal curve. In the light of the statistics and the shapes of the Kaplan Meier curves, there remains uncertainty as to if, or when, the OS curves for PP and AAP arms converge. This not only quite dramatically affects the anticipated cost effectiveness of abiraterone, it may also influence whether end of life criteria should be considered during for this assessment. Note that for the AAP arm the number at risk declines to 48 patients and so below 10% (n=557) from cycle 32, while for the PP arm the number at risk declines to 27 patients and so below 10% (n=275) from cycle 30 ( ).

The above needs to be considered within the context of the NICE DSU technical support document no. 14[5] which among other things suggests that:

- *Parametric models should be used, rather than restricted means approaches, unless data is almost entirely complete.*
- *Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two dimensional*

treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis.

The first point is relevant to the modelling of OS for both arms and of PFS in the PP arm, while the second is relevant to the selection of the Weibull or the truncated log normal for the modelling of OS in the PP arm.

- Equivalent survival and progression free survival with mitoxantrone compared to prednisolone

The manufacturer assumes OS and PFS for mitoxantrone were the same as for PP arm in the COU-AA-301 trial. For a discussion of these assumptions please see section 4.2.8 of this report.

- Quality of life

In response to ERG clarification question B2, the manufacturer supplied the central values for the FACT-P by arm for those on treatment, and for the end of therapy last assessment. ERG application of the manufacturer Adelphi[40] derived mapping function results in baseline estimates of [redacted] for AAP and [redacted] for PP. The end of therapy estimates that result are [redacted] for AAP and [redacted] for PP. These values cross check with those given by the manufacturer in Appendix 15 of the submission for the ITT population.

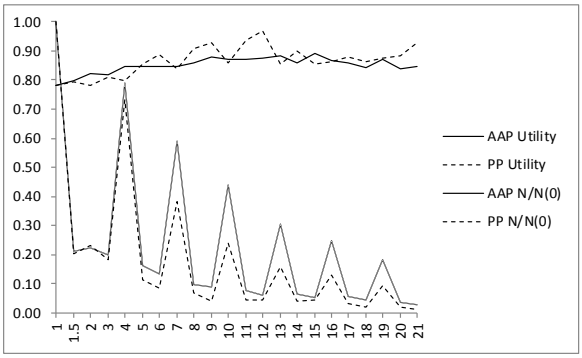
In response to ERG clarification question B2, the manufacturer supplied the mean FACT-P values collected during the pivotal trial cycles. Note that this appears to relate to the ITT patient population rather than the 1-prior chemo population. The figure below reports the utility values implied by the manufacturer's Adelphi mapping exercise coefficients coupled with the proportion reporting FACT-P. This assumes an age of 69 drawn from the manufacturer submission and an average of 27kgm^{-2} BMI as drawn from Sullivan and colleagues.[4] This also presents the proportion of the original sample reporting FACT-P, N_0, report FACT-P values at subsequent six monthly data points. Due to the 2:1 trial randomisation note that in the AAP arm N(0)≈[redacted][h] and in the PP arm N(0)≈[redacted].

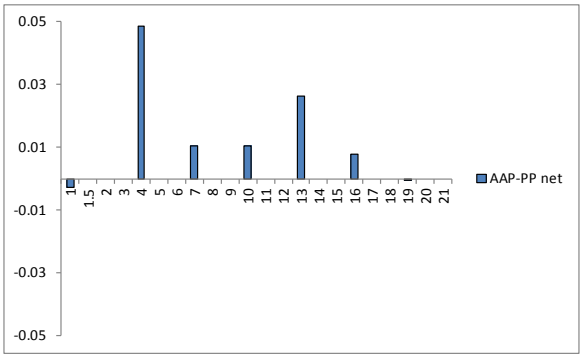
The response to ERG clarification question B2 does not define the cycle number along the x-axis. Table 7 of the manufacturer submission suggests that FACT-P was collected every 3 months for the first nine months and subsequently every six months. But applied to the above, this results in patient survival in excess of the KM curves. The ERG working assumption is that the cycles along the x-axis

[h] The number of patients reporting across the individual elements of the FACT-P varies, typically by one to two patients; e.g. at the first FACT-P data collection [redacted] reported the physical functioning well being while [redacted] reported the FACT-P subscale. Note that the ERG calculation of the FACT-P implied utility values does not attempt to correct for this, but simply multiplies the within cycle FACT-P subscale average value reported in the manufacturer response to ERG clarification B2 with its corresponding coefficient.

are 21 day cycles in line with KM curves such as Figure 7 of the manufacturer's submission and the cycle length of the manufacturer model, though based upon the Table 3 of the CSR the cycle length may be 28 days.

There is a clear declining trend in the number of patients reporting FACT-P values as would be expected. There are equally clear peaks every 3 cycles, when taking into account the additional cycle reported at 1.5 cycles. Interestingly, within the AAP arm the FACT-P derived utilities do not show any particular relationship to the peaks in the numbers reporting, but in the PP arm there is a clear negative effect ([redacted]).





[redacted]6[redacted]

In the following table, column 2 and 3 reports the KM PFS numbers at risk with% of these reporting FACT-P values, then column 4 and 5 the number of FACT-P responses with this as the % of those reporting at baseline), then column 6 and 7 the utility derived from applying the FACT-P mapping function to the average FACT-P values and finally the net utility (AAP - PP). But note again that it is not confirmed that the cycles of the model and the KM PFS curves necessarily relate to the same time frame as the FACT-P reported values ([redacted]).

[redacted]38[redacted]

Cycle	AAP PFS N	PP PFS N	AAP N	PP N	AAP Utility	PP Utility	Net Utility
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Even among the peak reporting periods it appears that there is a steady decline in the percentage of those who remain on treatment reporting FACT-P values: from an initial 95% to 63% by the 19th cycle. But there is a discrepancy in the number on treatment and the number reporting FACT-P

values in the 4th cycle for the PP arm, which may suggest that the ERG economic reviewer has misinterpreted the cycle numbers within the FACT-P data.

A simple weighted average of the post baseline utilities results in mean utilities for those on treatment and reporting FACT-P scores of [redacted] in the AAP arm and [redacted] in the PP arm: an increment from AAP of [redacted] Due to the obvious between peak effect within the PP arm, restricting this analysis to post baseline cycles of 4, 7, 10, 13, 16 and 19 results in weighted average utilities for those on treatment of [redacted] in the AAP arm and [redacted] in the PP arm: an increment from AAP of [redacted].

This is not immediately reconcilable with the increment from AAP over PP of [redacted] for the manufacturer base case from the multivariate analysis. The maximum effect estimated by the ERG of [redacted] occurs within cycle 4, but these observations account for only [redacted] of the total post baseline observations, or [redacted] of post baseline observations restricted to the peak reporting cycles.

However the manufacturer regression analysis is based upon changes from baseline scores rather than absolute values. Assuming a baseline value of [redacted] results in an on treatment utility within the AAP arm of for the ITT population of:

[redacted]

While the parallel calculation for the PP arm results in:

[redacted]

The difference between these is [redacted] as would be expected. But the estimate based upon the mean post baseline FACT-P values suggests an observed difference of only [redacted]. Retaining the *AAP On Tx ITT* utility of [redacted] as in the above would require that the *PP On Tx ITT* utility [redacted] to result in an observed average difference of [redacted]. This in turn would require the average baseline value within the PP arm to be [redacted], in that:

[redacted]

Caution must be exercised in interpreting the above, as it uses the mean FACT-P values among those reporting them subsequent to baseline. But it may indicate that among those reporting FACT-P data subsequent to baseline, the baseline utility among the AAP patients was lower than the baseline utility among PP patients. There may be the potential for this to result in bias if those with either a higher or lower initial utility were in some sense harder to treat in terms of experiencing a significant utility gain from treatment.

These considerations can also be used to illustrate an error in the handling of utilities, even if the mapping and regression analyses are accepted at face value. For the ITT analysis the manufacturer assumes no change in utility from a baseline value of [redacted] for those on treatment in the PP arm, and a utility increment of [redacted] for those on treatment in the AAP arm, to result in a utility on treatment of [redacted]. But as the above shows, the regression analysis implies respective on treatment values for the PP arm and the AAP arm of [redacted] and [redacted]. For the given utility for survival with progression of 0.500, this tends to exaggerate the benefit from remaining on treatment over both survival with progression and death by [redacted].

The utility values implied by the manufacturer mapping function appear at face value quite high and in comparison with those for mCRPC of the manufacturer review as supplied in Table 32 of the submission. For instance, the age specific EQ-5D average VAS score reported by Kind and colleagues[41] is between 0.800 and 0.750 for those ages between 60 and 79. This is in the context of a survey of the general population living in the community, of whom 475 respondents were aged between 60 and 69 and 406 were aged between 70 and 79. While based upon the EQ-5D VAS rather than the EQ-5D tariff, it seems surprising that the baseline value estimated from the FACT-P mapping function for the mCRPC patients within the trial is broadly similar.

ERG expert opinion suggests that due to the trial being oversubscribed, there may be a degree of selection in that the fittest, most aware and most mobile were possibly more likely recruited into the trial. There may also be some concern because the majority of patients within the Adelphi data set were receiving a course of chemotherapy, both their FACT-P scores and utilities would tend to be lower than those within the abiraterone trial. This could have result in the FACT-P mapping function derived from the Adelphi data being applied to FACT-P values outside the reliable range of the mapping function. This will increase the uncertainty around the derived utility values.

Note that Wu and colleagues[37] report a mean baseline EQ-5D utility among 276 mCRPC patients based upon the UK social tariff of 0.635, though this is skewed with a median of 0.73 and a skewness of -1.53. In other words there are a small number of patients who have a very low utility and who tend to pull the mean down below the median value. But these EQ-5D utilities are simple baseline utility values weighted using the UK social tariff, and not affected by any subsequent errors of analysis or reporting in the Wu regression analysis. Unfortunately, as noted by the manufacturer, Wu misreports the average baseline BMI as 72, the same as the average baseline age. But the other elements of the FACT-P data appear to be reasonable in terms of their central values. Putting these values through the manufacturer FACT-P mapping function, coupled with an assumed baseline age of 72 years and an ERG assumed BMI of 27kgm^{-2}, results in an estimated baseline utility for the Wu

cohort of [redacted]. This is somewhat above both the mean and the median baseline values reported by Wu.

The ERG report for the STA[3] of cabazitaxel as 2nd line chemotherapy reports that within this STA the manufacturer applies a utility decrement for the move from stable disease to progressive disease of 0.070 as drawn from the Sullivan reference,[4] coupled with a sensitivity analysis of a utility decrement of 0.085 as drawn from the Sandblom reference.[2] These are reviewed in more detail below.

Sullivan and colleagues[i] (2007)[4] estimated utilities among 280 men with hormone refractory prostate cancer from a variety of EU countries, Australia, Canada and the US with an average age of 72. Patients were eligible if they had a diagnosis of symptomatic M1 metastatic cancer. There is no obvious common baseline across patients, but the authors report mean PSA of 235[j] at baseline, with this rising to 345, 410 and 421 at months 3, 6 and 9 respectively. This compares to an average at baseline of 439ng/ml for AAP patients and 401ng/ml for PP patients within the pivotal denosumab trial. The average FACT-P prostate component score was 29.8 within the Sullivan cohort, while among UK patients it was 30.7. This compares to an average FACT-P prostate component score at baseline[k] within the data submitted by the manufacturer in response to ERG clarification B2 of 29.6 for AAP patients and 29.9 for PP patients. Sullivan and colleagues found that across all patients the average EQ-5D baseline utility was 0.635, while among UK patients it was 0.715, though it is not clear how the EQ-5D utility was calculated. Only the changes from baseline pooled across all patients are reported, with values taken from the graph suggesting decrements of 0.07 at 3 months, 0.06 at 6 months and 0.08 at 9 months.

Sandblom and colleagues[l] (2004)[2] studied the quality of life among Swedish men with an average age of 76 and prostate cancer in the year before death. The survey was conducted through a postal questionnaire, and of the 1,442 patients contacted 1,243 responded. Results were reported for both the EQ-5D VAS and the EQ-5D index score, though to what degree the calculation underlying the latter is specific to Sweden is unclear. Results were similar for both methods, with the average utilities reported for the EQ-5D index being approximately:

- 0.58 for 16 to 12 months prior to death
- 0.59 for 12 to 8 months prior to death
- 0.56 for 8 to 4 months prior to death
- 0.46 for 4 months prior to death to death

[i] Supported by Abbott
[j] Measurement units not given, but assumed by the ERG to be ng/ml as per the pivotal abiraterone trial.
[k] CYCLENUM 1 within the data
[l] Supported by Astrazeneca

95% confidence intervals were around ±0.10 though increase for 4 months prior to death to death to perhaps around ±0.12.

- HRQoL decrement for mitoxantrone while on treatment

The approach adopted applies a constant disutility for those on mitoxantrone treatment. This in turn assumes that the proportions with serious adverse events remain constant over the period of treatment; e.g. a constant 58% of mitoxantrone patients on treatment are experiencing neutropenia. But it appears that in the TROPIC trial,[31] 58% of mitoxantrone patients experienced neutropenia during the course of the study, though more than one event could occur per patient. Not controlling for the duration of a typical episode of neutropenia may have tended to exaggerate the overall QALY impact of adverse events for mitoxantrone.

The manufacturer convened consensus panel suggested that most adverse events would be of seven to fourteen days duration as outlined in the following table (Table 39).

Table 39. Manufacturer consensus panel: duration of adverse events

Adverse event	Duration	Adverse event	Duration
Neuropathy	Several months	Arthralgia	7-14 days
Neutropenia	7-14 days	Asthenia	Several months
Febrile Neutropenia	7-14 days	Diarrhea	7-14 days
Thrombocytopenia	7-14 days	Dyspnea	7-14 days
Anemia	7-14 days	Fatigue	Several months
Edema	7-14 days	Nausea	7-14 days
Hypokalemia	7-14 days	Vomiting	7-14 days
Hypertension	7-14 days		

The average duration of mitoxantrone therapy for the manufacturer base case is a little over five cycles, or fifteen weeks. With the admittedly arbitrary assumption that the adverse events listed as having several months duration correspond to this fifteen weeks, while the remainder are of the maximum 14 days duration, this would result in an approximate net loss of [redacted] QALYs from MP compared to AAP. The manufacturer's method appears to suggest a loss of [redacted] QALYs. The discrepancies are negligible at around 2% of the QALY gain estimated for AAP over MP and do not affect results.

- Direct drug cost

The manufacturer model applies half cycle correction to both treatment costs for the direct drug costs for the other ongoing costs. Half cycle correction is required for the ongoing costs such as those associated with SAEs and for QALYs. SAEs and deaths will be spread over the period of a cycle, hence the need to undertake half cycle correction to smooth between those present on day 1 of the cycle and those still present on day 21 of the cycle.

But it seems less reasonable for the direct drug costs. These are presumably prescribed with costs incurred among all those present on day 1 of the cycle.

The approximate impact of this within the model is to shift the prescription days from 0, 30, 60 etc. to 15, 45, 75 etc., (assuming an on treatment survival curve of daily cycles rather than three weekly cycles). This results in an approximate cost reduction of one half of one 3 weekly prescription: [redacted] for abiraterone with the PAS, though the impact of discounting will slightly increase this discrepancy.

A broad cross check of this can be undertaken by multiplying the percentage on treatment in cells J9:J183 of the manufacturer's model (*Model* worksheet) by the 3 weekly pro rata cost of abiraterone of [redacted] and by the relevant cost discount factors in cells AJ9:AJ183. Limiting the sum of this to those within the model horizon, this results in a discounted drug cost for abiraterone of [redacted] for the base case as compared to [redacted] when half cycle correction is applied, an increase of [redacted] or around 3%. But this may still understate the possible degree of drug wastage as it assumes availability of a 21 day pack size for abiraterone.

Unfortunately, the abiraterone pack duration of 30 days is not in line with the model cycle length of three weeks. As a consequence, a more formal analysis requires the on treatment survival curve for abiraterone to be revised from a three weekly cycle to a daily cycle. The ERG has approximated this by interpolating between each pair of 21 day data points with the assumption of a constant daily hazard between these two points. Prescriptions can then be specified at 30 day intervals, conditioned by the appropriate percentage remaining on treatment, the cost discount factor and the model time horizon. For the base case, this results in an estimated cost of [redacted] as compared to [redacted] when half cycle correction is applied, an increase of [redacted] or a little over 4%. This matches 30/21 * [redacted] = [redacted] to a reasonable degree. The ERG has not performed this calculation for the costs of prednisolone as the drug costs are small, or for mitoxantrone on the basis of ERG expert opinion suggesting it is of secondary interest.

- Administration and monitoring costs

The ERG calculations based upon manufacturer assumptions cross check with those of the manufacturer, though note that the following are monthly (52/12 = 4.33 weeks) and not 4 weekly costings (Table 40).

Table 40. ERG replication of monthly administration and monitoring costs

	Manufacturer estimate
Mitoxantrone on tx	£300
Abiraterone months 1-3	£279

Abiraterone months 4+	£150
Prednisolone	£114
Mitoxantrone off tx but PFS	£114
Off tx with progression	£146

The manufacturer response to clarification question B4 outlined that the consensus panel suggested the following resource use for abiraterone.

"*The Delphi panel suggested that patients receiving abiraterone would have an outpatient visit every 2 weeks for the first 3 months on treatment for blood tests and blood pressure checks.*

- *Who would they see at these visits (oncologist, GP, nurse)?* ***Oncologist***
- *Would they alternate who they see?* ***Only after first three months, would alternate between onc and nurse specialist***"

This would increase the monthly administration costs for abiraterone by around £129 per month or £97 per cycle for the first 3 months on the basis of a consultant led oncology OP appointment being £166. Note, however, that this reference cost is for the first attendance. Follow-up consultant led oncology OP appointments are given as £101 within NHS reference costs 2009-10.

On the assumption that the follow-up reference costs are more likely to be more representative since patients will be seeing an oncologist on an ongoing basis, applying the follow up appointment cost of £101 results in the following (Table 41).

Table 41. £101 for oncology OP visit monthly administration costs

	Monthly Cost
Mitoxantrone on tx	£205
Abiraterone months 1-3	£277
Abiraterone months 4+	£118
Prednisolone	£91
Mitoxantrone off tx but PFS	£91
Off tx with progression	£100

*All appointments assumed to be oncologist as per manufacturer consensus panel

- Other resource use

The manufacturer conducted an online survey to determine resource use, prior to conducting the consensus panel. The ERG requested the responses from the online survey in order to triangulate these results with those of the consensus panel in clarification question B4. The manufacturer has declined to supply this on the grounds that "*There was variation in the output and therefore the consensus meeting was used to agree estimates that could be used in the modelling*".

As already noted, the disaggregate MRU alluded to in ERG clarification question B5 has not been supplied, so has not been reviewed. ERG expert opinion views it as reasonable to expect unplanned medical resource use in the progression free period to be heavily weighted towards the end of this period.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

- KM cut-off points

The manufacturer base case applies a 10% cut-off within the OS KM curves, a 5% cut-off within the AAP PFS curve and retains the near complete KM curve for the PP PFS. These cut-offs are arbitrary. A range of cut-offs for the OS KM curves can be explored, varying this from 0% to 20%, with the manufacturer base case assumption of a constant hazard being applied thereafter. This is explored alongside the other dimension of the cut-off assumed for the AAP PFS curve: values of 0.0%, 2.5%, 5.0%, 7.5% and 10% have been explored in what follows. Only the cost effectiveness of AAP relative to PP is considered[m] (Figure 15).

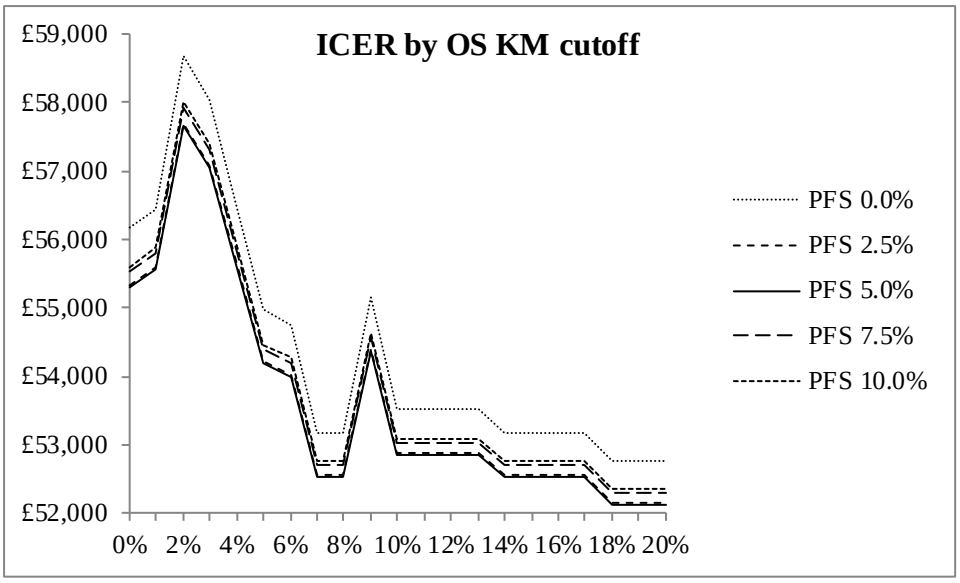


Figure 7. Cost effectiveness and KM cut-off points

For the OS KM cut-offs, after an initial increase in the ICER between 0% and 2% there is a reasonably consistent trend for the ICER plots to fall in the percentage cut-off with the exception of the spike at 9%. The 10% cut-off returns a relatively low ICER, with cut-offs beyond this point seeing some further but modest declines in the ICER.

The ICER plots for the AAP PFS cut-offs of 2.5% and 5.0% are very similar, the ICERs for the AAP PFS 5.0% cut-off being marginally lower than the ICERs for the 2.5% cut-off: around £30 per QALY. Similarly, the curves for the AAP PFS cut-offs of 7.5% and 10.0% are very similar, the ICERs for the AAP PFS 7.5% cut-off being lower than the ICERs for the 10.0% cut-off by between £50 and £90 per QALY. Apart from the possibility of a 0.0% cut-off, the impacts of different cut-offs for the AAP

[m] Implemented by setting cells K11 and K18 of the *Settings* worksheet equal to the relevant percentages.

PFS are relatively modest. But of the values tested by the ERG, the 5% cut-off provides the lowest set of ICERs for AAP versus PP.

When the manufacturer's 10% cut-off exponential extrapolation is extended back to t_0, the fit to observed KM was inferior to that with a Weibull parametric fit (Appendix 7).

- Most appropriate form for OS and PFS modelling

There is some uncertainty around what are the most appropriate forms for extrapolating OS and PFS. The manufacturer justification for the data cut of the Kaplan Meier centres around the uncertainty due to the limited number of patients remaining. This uncertainty would seem to relate to the absolute number of patients remaining rather than the percentage, and given the 2:1 trial randomisation between AAP and PP there may be an argument for applying double the percentage data cut within the treatment of the PP KM curves (Table 42).

Table 42. Additional ERG sensitivity analyses on OS and PFS: 1 prior chemo

	Overall survival		Progression free survival		ICER vs	
	OS AAP	OS PP	PFS AAP	PFS PP	PP	MITOX
Base	KM, 10%, h(t)=k	KM, 10%, h(t)=k	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£52,851	£43,437
SA1	KM, 10%, h(t)=k	KM, 10%, h(t)=k	KM, 5%, h(t)=k	KM, 5%, h(t)=k	£54,658	£48,567
SA2	KM, 10%, h(t)=k	KM, 20%, h(t)=k	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£54,731	£48,269
SA3	KM, 10%, h(t)=k	KM, 20%, h(t)=k	KM, 5%, h(t)=k	KM, 10%, h(t)=k	£56,228	£49,887
SA4	KM, 20%, h(t)=k	KM, 20%, h(t)=k	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£52,126	£45,980
SA5	Weibull	Weibull	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£56,339	£49,691
SA6	Weibull	Weibull	Weibull	KM, 0%, h(t)=1	£57,111	£50,191
SA7	**Weibull**	**Weibull**	**Weibull**	**Weibull**	**£58,116**	**£51,279**
SA8	Weibull	LogNorm (trunc.)	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£64,159	£56,691
SA8	Weibull	LogNorm (trunc.)	Weibull	Weibull	£66,820	£59,157
SA9	Weibull	Weibull	LogLogistic	LogLogistic	£56,211	£49,984
SA10	Weibull	LogNorm (trunc.)	LogLogistic	LogLogistic	£63,942	£57,057
SA11	LogNorm	LogNorm	KM, 5%, h(t)=k	KM, 0%, h(t)=1	£44,578	£39,425

KM – Kaplan Meier, x% KM data cut, h(t)=k from baseline to data cut assumed for extrapolation beyond data cut
LogNorm (trunc.) assumed to follow AAP OS weibull at cross over at cycle 49

Note that the sensitivity analysis that applies the log normal to both OS curves results in survival at two years of 38% for AAP and 26% for PP. This is in contrast to the KM curves which suggest 33% and 25% respectively, illustrating the poorness of fit of the log normal for OS in the AAP arm.

The above suggests that a key sensitivity of the model is whether it is reasonable to assume a truncated log normal distribution for the OS curve in the PP arm. Is it reasonable to expect overall survival curves to converge at around 2 years 9 months, when around 15% of patients are estimated to still survive?

Because the log normal and log logistic survival curves for OS and PFS result in a number of curves crossing and having to be truncated, the remaining sensitivity analyses assume Weibull curves for OS and for PFS for both AAP and PP; i.e. **SA7** in the above Table 42. In the light of the DSU briefing document,[5] and due to the centrality of this, the corresponding values and their implementation within the electronic model are summarised in Appendix 6.

- Additional ERG sensitivity analyses

For the following sensitivity analyses, the baseline of the analysis applies the following:

- Weibull parametric fits for OS and PFS curves
- The change from baseline utility regression applies the baseline utility coefficient
- The administration costs are based upon £101 per oncology OP consultation
- Abiraterone consultations during 1st 3 months apply the £101 per oncology OP consultation
- Mitoxantrone £187 per dose and £212 per administration
- Mitoxantrone lambda revised to 4.019 to yield a median of 4 cycles
- Post progression percentage on bisphosphonates as per PFS percentage

This is a revised baseline rather than base case, the results of which for the 1-prior updated analysis results are as follows (Table 43 and Table 44).

Table 43. ERG revised baseline disaggregate outcomes

	APP	PP	MITOX
Undiscounted survival years AAP net	[redacted]	[redacted]	[redacted]
Undiscounted PFS years AAP net	[redacted]	[redacted]	[redacted]
Costs			
Direct drug cost Concomitant drug cost Other costs Terminal care costs	[redacted]	[redacted]	[redacted]
Total AAP net	[redacted]	[redacted]	[redacted]
QALYs AAP net	[redacted]	[redacted]	[redacted]

Table 44. ERG revised baseline cost effectiveness

	Cost	net	QALYs	net	ICER
PP	[redacted]		[redacted]		
MITOX		[redacted]		[redacted]	ext. dom.
AAP					£60,084

The ERG has additional concerns about the appropriateness of applying half cycle correction to the direct drug costs. Removing this would increase net costs by around [redacted] and further worsen the cost effectiveness by around £2,500 per QALY.

The following sensitivity analyses are undertaken (Table 45)

- Truncated lognormal modelling of OS for PP
- £106 per week for progression free unplanned medical resource use[n]
- A fixed cost for unplanned medical resource use during survival with progression
- A utility increment from being on treatment with AAP over PP of [redacted]
- A utility increment from being on treatment with AAP over PP of [redacted]
- A utility for prednisolone progression free survival of 0.500 + ([redacted] - [redacted]) = [redacted]
- A utility for survival with progression of [redacted]
- A utility for prednisolone on treatment of 0.715 and for survival with progression of 0.645

Table 45. ERG exploratory sensitivity analyses

		PP	MP
Baseline		£60,084	ext. dom.
Overall survival approach	Log Normal for PP	£70,217	ext. dom.
Unplanned PFS MRU	£106 per week	£67,554	ext. dom.
Survival with progression MRU	Fixed cost	£60,492	ext. dom.
HRQoL AAP - PP	[redacted]	£65,911	ext. dom.
HRQoL AAP - PP	[redacted]	£63,281	ext. dom.
HRQoL PP on Tx	[redacted]	£72,469	ext. dom.
HRQoL off Tx	[redacted]	£63,326	ext. dom.
HRQoL PP on Tx, off Tx	0.715, 0.645	£67,140	ext. dom.

- Anticipated increase in overall survival

Due to the possibility that end of life considerations may be relevant to this assessment, the proportions of the overall survival that occur within the period of the trial and the proportion that are extrapolated can be presented. The manufacturer base case extrapolates from the Kaplan Meier curves at the 10% cut-off, which can be taken as being from cycle 31 for AAP and from cycle 29 for PP as per Base[1] in the following table (Table 46). The remaining presentations assume extrapolation is beyond the period of the trial, from cycle 37 of the model.

Table 46. Additional AG sensitivity analyses on OS: net undiscounted life years 1 prior chemo

	Overall survival		LY AAP			LY PP			net LY		
	OS AAP	OS PP	LY^{WT}	LY^{EX}	**LY**	LY^{WT}	LY^{EX}	**LY**	LY^{WT}	LY^{EX}	**LY**
Base[1]	KM	KM	[redacted]								
Base[2]	KM	KM									
SA5	Weibull	Weibull									
SA10	Weibull	LogNorm(trunc)									

[n] Implemented by adding £4.33*106=£459to each of cells *E76:E80* and setting cells E93:E95 equal to zero within the Cost Inputs worksheet.

SA11	LogNorm	LogNorm	[redacted]
			LY: total modelled survival, LY^{EX}: extrapolated, LY^{WT}: within trial

5.5 Summary and conclusions

The manufacturer presented a relatively straightforward comparison of AAP with PP based upon the KM curves for both OS and PFS. This concentrated upon the updated analysis for the one prior chemotherapy patient population, which the ERG views as appropriate. Since progression was not formally measured within the trial, treatment continuation was taken to be synonymous with PFS. The KM OS curves were truncated when the number at risk dropped to 10%, with the constant hazard implied up to this point being used for extrapolation. The KM AAP PFS curve was truncated when the number at risk dropped to 5%, with the constant hazard implied up to this point was used for extrapolation. The KM PP PFS was almost complete by the end of the trial, and no extrapolation was applied.

The model applied a 10 year time horizon which was in effect lifetime, coupled with a 3 weekly cycle to be in line with the MP dosing schedule.

The manufacturer submission was largely in line with the NHS reference case, though MP effectiveness was by assumption, and utility values were based upon FACT-P data.

The effectiveness estimates for MP were not drawn from a systematic review and mixed treatment comparison. Rather, both the OS and the PFS for MP were assumed to be the same as PP. Treatment duration for MP was not synonymous with PFS, and was based upon a median of 5 cycles and a maximum of 10 as drawn from the TROPIC trial.[31] The ERG accepts that there is no evidence for a survival advantage from MP over PP. It is less clear that there is no evidence of a PFS advantage from MP over PP, though the manufacturer did explore this within a sensitivity analysis.

Utility data was not collected among patients using the EQ-5D. The pivotal trial collected FACT-P data. A separate Adelphi database supplied FACT-P and EQ-5D values for mCRPC patients. This enabled the manufacturer to estimate a mapping function from FACT-P to EQ-5D utility values, these latter being estimated using the standard UK tariff. This mapping function was then applied to the trial FACT-P data. This supplied the estimates for the on-treatment, progression free utilities: [redacted] for AAP and [redacted] for PP. The value for MP PFS was assumed to be that of AAP, conditioned by the higher rates of adverse events while on MP treatment.

Trial based end of therapy FACT-P values were not used to inform the utility for survival with progression. A value of 0.500 was drawn from a separate reference within the literature.

Resource use was divided into planned resource use while progression free, and unplanned resource use associated with adverse events and progression. Planned resource use consisted of the direct drug, administration and monitoring costs. The rates for this were drawn from a manufacturer convened consensus panel of experts. The resulting resource use was viewed as reasonable by ERG expert opinion.

Unplanned resource use for the progression free period was drawn from data collected during the trial. This was restricted to those patients who had progressed during the trial. It was further restricted to those with non-zero unplanned resource use data, though this restriction was equally balanced between the arms. Since the main driver of this resource use was hospitalisation, with hospitalisation being closely linked to progression, the manufacturer applied a fixed cost of [redacted] per patient for unplanned resource use during the progression free period.

Additional resource use for chemotherapy post progression and terminal care was included, but this had very little impact upon results.

The central estimate was that with the PAS, MP was extended dominated by AAP. The cost effectiveness of AAP against PP was estimated as £52,851 per QALY. Probabilistic estimates were in line with this and suggested that below a willingness to pay of £40,000 per QALY there was virtually no probability of AAP being cost effective, while above a willingness to pay of £70,000 per QALY there was little uncertainty that AAP would be cost effective.

Clarifications by the manufacturer indicated that the Weibull was the best parametric fit for AAP OS, the lognormal for PP OS, and the log logistic for both AAP PFS and PP PFS. Applying these within the manufacturer model resulted in the PP OS curve meeting the AAP OS curve at the 49th cycle. The manufacturer assumption for this sensitivity analysis, though not presented within the submission, was that the PP OS curve would then follow the AAP OS curve. This worsened the cost effectiveness of AAP compared to PP to £64,159 per QALY.

The application of log logistic curves for the PFS had a limited impact, slightly improving the cost effectiveness of AAP. But similar difficulties arose with curves crossing due to the long tails.

In the light this and the NICE DSU technical document 14,[5] the ERG views the application of Weibulls for all OS and PFS curves as the most appropriate.

The FACT-P mapping function was based upon the restricted set of patients who reported FACT-P values at baseline and subsequent to it, enabling changes from baseline to be estimated. A large proportion of these were from relatively early in the trial. It also appears that the baseline values of those reporting FACT-P values subsequent to baseline may have been higher in the PP arm than the AAP arm. Those reporting subsequent to baseline in the PP may have shown a smaller change due to having less severe disease.

There may be additional concerns around the average FACT-P values within the Adelphi data set being somewhat lower than those within the trial. The mapping function may have been applied outside the range of FACT-P values for which it can reliably estimate utilities. The values of [redacted] for AAP and [redacted] for PP appear quite high when likely comorbidities, such as bone metastases, are borne in mind.

ERG expert opinion viewed the planned resource use as reasonable. ERG expert opinion also agreed that unplanned medical resource use for progression free survival would be mainly for hospitalisation, and that this would be concentrated at the end of the progression free period. But it is less obviously reasonable to have treated unplanned resource use during progression free survival as a fixed cost. There is further uncertainty around this, as data used to support this also appears to have the same progression free duration for the AAP arm as the PP arm.

Applying the Weibull estimates to all OS and PFS curves, and correcting some additional cost and utility elements to be in line with the manufacturer stated assumptions, resulted in AAP still dominating MP. It resulted in the cost effectiveness of AAP compared to PP of £60,084 per QALY.

Further ERG univariate sensitivity analyses around unplanned medical resource use resulted in the cost effectiveness of AAP compared to PP ranging between £60,492 per QALY and £67,554 per QALY. Sensitivity analyses bringing utility estimates into line with other sources resulted in the cost effectiveness ranging between £63,281 per QALY and £72,469 per QALY. Applying a truncated lognormal functional for PP OS resulted in a cost effectiveness estimate of £70,217 per QALY.

6. END OF LIFE

The manufacturer makes the following case that EoL criteria should be considered. The following evidence to demonstrate whether this submission meets all or some of the criteria was provided during the clarification process.

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

The prognosis of mCRPC patients is poor; the five-year survival rate for those with metastatic disease is significantly lower (31%) than compared to in patients with non-metastatic disease (almost 100%). The control arms of the COU-AA-301 and TROPIC studies indicate that after 1st line docetaxel treatment patients treated with prednisolone or mitoxantrone have a short, average life expectancy of approximately one year.

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

Of the 4,400 mCRPC patients estimated to receive docetaxel in the UK, it is estimated that approximately 75% of these men would be eligible for treatment with abiraterone acetate (3,300 men). It is estimated that no more than 50% of these men would actually receive treatment with abiraterone acetate. These patient numbers are similar to patient numbers in other disease areas that have met NICE EoL criteria.

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

Abiraterone acetate offers the mCRPC patient population a 4.6 month increase in median overall survival (OS) compared to prednisolone, representative of best supportive care (BSC). This result is aligned with the economic model which estimates that the expected mean OS for patients in England and Wales would be [redacted] years or [redacted] months.

To summarise, abiraterone acetate should be considered to meet end of life criteria as it extends life by over 4.5 months in this patient population, for whom there are no other NICE approved treatment options with evidence of improved survival. In the absence of abiraterone acetate, this patient population (estimated to be approximately 3000 patients), has a very short life expectancy of less than one year.

7. CONCLUSIONS

A single good quality double blind RCT comparing AAP versus PP provided convincing evidence for the effectiveness of abiraterone in terms of prolonged survival, delayed progression and improved HRQoL while on treatment, for patients with mCRPC who had progressed during or after docetaxel therapy. These results held for the whole trial population and for the subpopulation who had received only docetaxel but no other type of chemotherapy which the manufacturer considered most relevant to the decision problem.

The evidence base lacked studies allowing direct or indirect comparison of abiraterone plus prednisolone versus mitoxantrone (with or without prednisolone). It appears that currently in the UK mitoxantrone is rarely used in first line or second line treatment of patients with mCRPC.

Abiraterone is regarded as an innovative therapy, is orally administered and therefore convenient for patient and NHS, [redacted], its adverse event profile is relatively mild in the context of mCRPC and chemotoxic therapies.

The manufacturer's base case deterministic economic analysis delivered ICERs of £46,617/QALY and £52,852/QALY for AAP versus mitoxantrone (with or without prednisolone) and versus PP respectively. In the manufacturer's probabilistic analysis, at a willingness to pay of £50,000/QALY, AAP had a [redacted] probability of being cost effective relative to PP and mitoxantrone (with or without prednisolone). The ERG's preferred baseline ICER estimate was £60,084/QALY. This higher ICER resulted from relatively minor changes to model inputs including: the selection of different survival modelling; revised oncology follow-up reference costs and a small correction to the estimate of utility for the progression-free state. The ERG conducted sensitivity analyses around its baseline ICER in order to explore issues considered relevant to the decision problem and cost effectiveness of AA. These all generated ICERs greater than the ERG baseline estimate.

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Appendices

Appendix 1 Quality of the study

Table 47. Risk of bias table for de Bono et al 2011 study[20]

Criteria	Description	Judgement
Adequate sequence generation	Participants were randomised in a 2:1 ratio using a centralised Interactive Web Response System (IWRS) and were stratified by baseline ECOG performance status score (0-1 or 2), presence or absence of clinically significant pain (using BPI-SF), number of previous chemotherapy regimens (1 vs. 2) and documented type of prostate cancer progression at entry [an increase in the PSA concentration only versus radiographic evidence of progression with or without an increase in the PSA concentration]	Yes
Allocation concealment	Randomisation using a centralised IQWS	Yes
Blinding	Double blind; Participants and investigators were blinded to the study drug. Placebo matched abiraterone acetate tables in size, colour and shape. All participants, family members, study personnel and members of the Independent Data Monitoring Committee (IDMC) remained blind to treatment assignment until completion of the study	Yes
Incomplete outcome data addressed	ITT analysis for efficacy data and modified ITT for safety population. Adequate description of losses to follow-up not given in the published paper.	Yes
Free of selective reporting	All the pre-specified and predefined outcomes were reported	Yes
Groups comparable at baseline	Baseline demographic and other characteristics were well-balanced between the two treatment groups	Yes
Sample size calculation	A planned sample size of approximately 1158 participants provided 85% power to detect a hazard ratio (HR) of 0.80 for death in the group receiving AAP as compared with the group receiving PP	Yes

Appendix 2 Ongoing studies

1. **NCT00544440:**

A phase II study of abiraterone acetate (1000 mg orally/day) in combination with prednisolone (5 mg orally b.i.d) in patients with mCRPC. Duration of the trial is one year. Start date October 2007, estimated completion date December 2011 [last updated February 15 2011]. Primary outcome measure is to learn how abiraterone acetate may affect the levels of testosterone and DHT in the bone marrow of patients with prostate cancer. Secondary measures include: explore potential association between serum PSA with bone marrow androgen levels; explore correlation between levels of circulating androgens and those in the bone marrow before and during treatment; collect and archive bone marrow.

http://clinicaltrials.gov/ct2/show/NCT00544440

2. **NCT00473512:**

A phase I/II open label study of continuous once-daily administration at recommended dose of abiraterone acetate in patients with HRPC. The starting dose for abiraterone acetate for the dose escalation phase will be 250 mg whereas the planned doses are 250 mg/day, 500 mg/day, 750 mg/day, 1000 mg/day and 2000 mg/day. Duration of the trial: not given. Start date December 2005, estimated completion date December 2009 [last updated January 20 2009, updated by clinicaltrials.gov on Nov 2 2011- current status: *'the recruitment status of this study is unknown because the information has not been verified recently'*]. Primary outcome measures include safety and tolerability of the drug and effect on testosterone levels.

http://clinicaltrials.gov/ct2/show/NCT00473512

3. **NCT01217697:**

An open label study of abiraterone acetate (1000 mg orally/day) in combination with prednisone (5 mg orally b.i.d), in patients with mCRPC who have progressed after taxane-based chemotherapy. Duration of the trial: signing of informed consent to the time of end of study visit i.e. 30 days after discontinuation of study drug. Start date November 2010, estimated completion date October 2014 [last updated July 14 2011 – *'currently recruiting participants'*]. Primary outcome measures include number and type of adverse events reported by the investigator or the patient.

http://clinicaltrials.gov/ct2/show/NCT01217697

4. **NCT01393730:**

A phase II open label trial of abiraterone acetate (1000 mg orally/day) in combination with dutasteride (3.5 mg orally/day) and prednisone (5 mg orally/day) in patients with mCRPC. Duration of the trial:

2 years. Start date August 2011, estimated completion date June 2013 [last updated July 28 2011 – *'study not yet open for participant recruitment'*]. Primary outcome measure is to analyse possible AR (androgen receptor) related mechanisms of abiraterone acetate resistance in serial CRPC metastasis biopsies. Secondary outcome measures include: serum levels of testosterone, DHT and androgen precursors at baseline and at progression; PSA response; PSA response duration on abiraterone acetate-prednisolone/dutasteride; response of measurable disease; time to progression of bone lesions or measurable disease (RECIST); toxicity; correlated presence of AR amplification; serum androgens and CTC levels; evaluation of methods for using CTCs for RNA based expression profiling of AR and AR regulated genes as an exploratory endpoint.
http://clinicaltrials.gov/ct2/show/NCT01393730

5. **NCT00638690: [**Other study ID numbers : **CR016924; COU-AA-301]**

A phase III, randomised, double-blind trial of abiraterone acetate (1000 mg orally/day) in combination with prednisone/prednisolone (b.i.d) compared against placebo (4 tabs) plus prednisone/prednisolone (b.i.d) in patients with mCRPC who have failed one or two chemotherapy regiments (at least one of the previous chemotherapies must have contained docetaxel). Start date April 2008, estimated completion date December 2012 (last updated August 19 2011). Primary outcome measures include overall survival. Secondary outcome measures include: proportion of patients achieving a PSA decline of 50% and time to PSA progression; PFS (based on imaging studies).
http://clinicaltrials.gov/ct2/show/NCT00638690

6. **NCT00473746:**

An open label dose-escalation phase I/II trial of abiraterone acetate (1000 mg orally/day) and prednisoone (5 mg orally b.i.d) in patients with HRPC. Start date July 2006, estimated completion date December 2011 [last updated February 15 2011]. Primary outcome measures include: phase I – to determine maximum tolerated dose of abiraterone acetate administered orally on a continuous basis; phase II – to assess safety and tolerability of abiraterone acetate with concurrent prednisone and to assess additional parameters for anti-tumor activity and clinical benefits. Secondary outcome measures include: phase I – safety and tolerability; pharmacokinetics; pharmacodynamics; need for steroids; preliminary anti-tumour activities; phase II – safety and tolerability; anti-tumour activity and clinical benefits.
http://clinicaltrials.gov/ct2/show/NCT00473746

7. **NCT01309672:**

A phase II trial of abiraterone acetate (orally daily on days 1 to 28 and repeated every 28 days in the absence of disease progression or unacceptable toxicity) in patients with prostate cancer who have undergone initial hormone therapy. Patients also receive androgen blockade with GNRH agonists like

goserelin acetate or leuprolide acetate or a GNRH antagonist (degarelix) per treating physician and these drugs can be given until evidence of disease progression. Bilateral orchiectomy can also be performed. After completion of treatment, patients are followed up every 3 months for 1 year and then every 6 months for up to 3 years. Start date September 2011, estimated completion date August 2012 [last updated November 1 2011- *'currently recruiting participants'*]. Primary outcome measures include rates of undetectable PSA. Secondary outcome measures include overall survival and objective PFS; PSA partial response and toxicity of abiraterone acetate.
http://clinicaltrials.gov/ct2/show/NCT01309672

8. **NCT01400555:**

A phase Ib, open label, safety study of abiraterone acetate (to evaluate the maximum safe dose) in combination with docetaxel (60 or 75 mg/m^2) plus prednisolone (5 mg b.i.d) in patients with mCRPC. The dose of abiraterone acetate is escalated from 500 mg to 1000 mg per day until the maximum tolerated does (MDT) is determined. Therefore it is administered as a single daily dose of 550 or 750 or 1000 mg. Start date September 2011, estimated completion date April 2014 [last updated October 6 2011 – *'not yet open for participant recruitment'*]. Primary outcome measures include proportion of patients with a dose-limiting toxicity. Secondary outcome measures include proportion of patients with PSA response, time to PSA progression, objective response rate, radiographic PFS and overall survival.
http://clinicaltrials.gov/ct2/show/NCT01400555

9. **NCT00485303:**

A phase II, open label trial of abiraterone acetate (1000 mg orally/day) in combination with prednisone/prednisolone (5 mg orally b.i.d) in patients with advanced prostate cancer who have failed androgen deprivation and docetaxel-based chemotherapy. Start date June 2007, estimated completion date June 2011 [last updated February 2011]. Primary outcome measures include PSA response during treatment.
http://clinicaltrials.gov/ct2/show/NCT00485303

10. **NCT00474383:**

A phase II, open label trial of abiraterone acetate (1000 mg orally/day) in patients with advanced prostate cancer who have failed androgen deprivation and docetaxel-based chemotherapy. Start date December 2006, estimated completion date June 2011 [last updated February 15 2011]. Primary outcome measures include anti-tumour effects. Secondary outcome measures include safety of the drug.
http://clinicaltrials.gov/ct2/show/NCT00474383

11. **NCT01186484:**

A phase I study of abiraterone acetate in patients with CRPC. Start date June 2010, estimated completion date January 2012 [last updated July 14 2011 – *'currently recruiting participants'*]. Primary outcome measures include the pharmacodynamics (serum concentrations of corticosterone, testosterone, DHEA-S, 11-deoxycorticosterone) at days 1, 2 and 8 of cycle 1 and the number of patients reporting adverse events as a measure of safety at 4 weeks. Secondary outcome measures include plasma concentrations of abiraterone acetate and abiraterone at 4 weeks, rates of decrease of PSA >50% (maximum 52 weeks) and tumor regression in patients with measurable lesions (maximum 52 weeks).
http://clinicaltrials.gov/ct2/show/NCT01186484

12. **NCT00887198:** [Other study ID number**: COU-AA-302**]

A phase III, randomised, double-blind trial of abiraterone acetate (1000 mg orally/day) plus prednisone/prednisolone (5 mg orally b.i.d) compared against placebo plus prednisone/prednisolone in asymptomatic or mildly symptomatic patients with mCRPC. Start date April 2009, estimated completion date April 2014 [last updated May 21 2010]. Primary outcome measures include overall survival and PFS every 3 months while on study and during follow-up.
http://clinicaltrials.gov/ct2/show/NCT00887198

13. **NCT01424930:**

A phase II, open label safety study of abiraterone acetate (1000 mg orally/day) and prednisone (5 mg orally b.i.d) in patients with mCRPC either on a low-fat or high-fat diet. Start date September 2011, estimated completion date September 2013 [last updated September 8 2011 – *'study not yet open for participant recruitment'*]. Primary outcome measures include toxicity related to dosing after low-fat or high-fat meals, physical exams, vital sign measurements, hematology and chemistry assessments. Secondary outcome measures include plasma levels of study agents.
http://clinicaltrials.gov/ct2/show/NCT01424930

14. **NCT00638690:**

A phase III, randomised, double-blind study of abiraterone acetate (1000 mg orally/day) and prednisone/prednisolone (b.i.d) compared against placebo plus prednisone in patients with mCRPC who have failed docetaxel-based chemotherapy. Start date April 2008, estimated completion date December 2012 [last updated August 19 2011]. Primary outcome measures include overall survival. Secondary outcome measures include proportion of patients achieving a PSA decline of 50% and time to PSA progression, and PFS (based on imaging studies).
http://clinicaltrials.gov/ct2/show/NCT00638690

15. **NCT01217697:**

An open label study of abiraterone acetate (1000 mg orally/day) plus prednisone (5 mg orally b.i.d) in patients with mCRC who have progressed after taxane-based chemotherapy. Start date November 2010, estimated completion date October 2014 [last updated July 14 2011 – '*currently recruiting participants*']. Primary outcome measures include the number and type of adverse events reported by the investigator or the patient.

http://clinicaltrials.gov/ct2/show/NCT01217697

16. **NCT00473746:**

A phase I (dose escalating)/II (1000 mg orally/day), open label, pharmacokinetics, pharmacodynamics , anti-tumor activities and safety study of abiraterone acetate in combination with prednisone (5 mg orally b.i.d) in patients with HRPC. Start date July 2006, estimated completion date December 2011 [last updated February 15 2011]. Primary outcome measures include: phase I – to determine maximum tolerated dose of abiraterone acetate; phase II – to assess proportion of patients achieving a >50% PSA decline during therapy with concurrent prednisone. Secondary outcome measures include: phase I – safety/tolerability; pharmacokinetics; pharmacodynamics; need for steroids; preliminary anti-tumour activities; phase II – safety and tolerability; parameters for anti-tumour activity and clinical benefits.

http://clinicaltrials.gov/ct2/show/NCT00473746

17. **NCT00474383:**

A phase II open label study of abiraterone acetate in patients with androgen independent metastatic prostate cancer who have failed docetaxel based chemotherapy, to evaluate the anti-tumour effects as measured by the proportion of patients achieving a PSA decline of >50% according to PSAWG criteria. Start date December 2006, estimated completion date June 2011 [last updated February 15 2011]. Primary outcome measures include anti-tumour effects. Secondary outcome measures include safety.

http://clinicaltrials.gov/ct2/show/NCT00474383

18. **NCT01254864:** [Other study ID numbers: **2010-0070**]

A phase II trial in patients with prostate cancer to know whether adding either sunitinib malate or dasatinib to the combination of abiraterone acetate and prednisolone can help. Start date March 2011, estimated completion date March 2014 [last updated September 15 2011 – '*currently recruiting participants*']. Primary outcome measures include overall final failure time (12 weeks) defined as time to final failure in up to 3 courses from the start of therapy.

http://clinicaltrials.gov/ct2/show/NCT01254864

19. NCT00600535:

A phase I trial of abiraterone acetate (100 mg orally/day) in capsule formulation compared against tablet formulation in patients with prostate cancer under fasted and fed conditions. Participants also received prednisone/prednisolone (5 mg orally b.i.d). Start date July 2007, estimated completion date March 2010 [last updated January 22 2009 – '*recruitment status unknown as the information has not been verified*']. Primary outcome measures include pharmacokinetics at 14 weeks. Secondary measures include safety and efficacy of continuous dosing at 12 months.
http://clinicaltrials.gov/ct2/show/NCT00600535

Appendix 3 Results for progression presented in the manufacturer's clarification document.

Appendix 4 PROVENGE and MDV3100

PROVENGE (sipuleucel-T):

Provenge has been approved by FDA for use in the treatment of asymptomatic or minimally symptomatic mCRPC (hormone refractory).[42] It is an autologous cellular immunotherapy. It is prepared by using patient's peripheral blood mononuclear cells which is collected via a standard leukapheresis procedure approximately 3 days before the infusion date. The cells are then sent to a special manufacturing centre (currently located only in USA however a centre in Europe is opening soon) where they are processed further to make them ready for infusion. A single dose of PROVENGE consists of at least 50 million autologous CD54+ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP. The recommended therapy of PROVENGE is a three complete doses at an interval of approximately two weeks.

The efficacy data of PROVENGE comes from a three similar randomised, double-blind, placebo-controlled multicentre trials. The intervention arm received PROVENGE while the control arm received autologous peripheral blood mononuclear cells that had not been activated. The median overall survival in study 1 was better in the PROVENGE group compared to the control group (25.8 vs. 21.7 months, difference of 4.1 months). In study 2, the results were similar to the previous study (25.9 vs. 21.4 months, difference of 4.5 months). The third study was terminated before completion of planned accrual.

The most frequently reported adverse events in the trial were chills, fatigue, fever, back pain, nausea, joint ache and headache. Approximately 68% of these events in the PROVENGE group were mild to moderate in intensity. The incidence of grade 3 (severe) and grade 4 (life-threatening) adverse events was similar between the groups (23.6% and 4% respectively in the PROVENGE group compared to 25.1% and 3.3% in the control group). Similarly, grade 5 (fatal) events were similar between the groups. The most frequently (approx. 2%) reported grade 3 to 5 events in the PROVENGE group were back pain and chills.

The incidence of serious adverse events was also similar between the groups (24% in the PROVENGE vs. 25.1% in the control group). The serious events in the PROVENGE group included acute infusion reactions and cerebrovascular events (hemorrhagic and ischemic strokes -3.5% in the PROVENGE vs. 2.6% in the control). Therefore, the manufacturer has recommended to look for signs and symptoms of acute transfusion reactions and also any symptoms of cardiac arrhythmia.

The cost of each dose is $31,000.[43]

MDV3100

This is an orally taken androgen-receptor antagonist. In a phase I/II trial of MDV3100 among patients with diagnosis of mCRPC and a mean age of 68 years (range 44 to 93 years), the drug demonstrated positive effects among these patients.[44] It was administered orally at a starting dose of 30 mg/day and then escalated up to 600 mg. The maximum tolerated dose was found to be 240 mg. The reduction in PSA of 50% or more occurred in 56% (n=78) of patients. The median time to radiological progression was 47 weeks. Approximately one fourth patients (n=13, 22%) showed positive response in soft tissues while more than half of the patients (56%) demonstrated stable bone disease. The PET scan of 22 patients also showed reduced levels of F-fluoro-5α-dihydrotestosterone binding at doses from 60 mg to 480 mg per day. The most frequently reported grade 3 or 4 adverse events included dose-dependent fatigue (11%), that resolved on dose reduction.

A phase III trial of MDV3100 is going on. The study will compare MDV3100 against bicalutamide in patients with mCRPC who have progressed while on LHRH agonist/antagonist or after receiving a bilateral orchiectomy. The study is currently recruiting participants. It is anticipated to be complete by September 2013. The primary outcome measure includes progression free survival. Secondary outcome measures include PSA response, time to PSA progression and safety of the drug. [http://clinicaltrials.gov/ct2/show/NCT01288911]

Appendix 5 PRESS checklists

PRESS checklist- Clinical effectiveness section (Section 4.1.1)

1. Translation: Is the search question translated well into search concepts?

☑ Adequate

☐ Needs revision - Provide an explanation or example

_____

_____

2. Operators: Are there any mistakes in the use of Boolean or proximity operators?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

3. Subject headings: Are any important subject headings missing or have any irrelevant ones been included?

☑ Adequate, *but see note below*

☐ Needs revision Provide an explanation or example

_____*The Embase and Medline database searches were combined and subject headings for Embase were applied, some of these were not applicable in Medline but they should have mapped over OK.*_____

____ _____

4. Natural language: Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation used optimally?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

5. Spelling & syntax: Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

6. Limits: Do any of the limits used seem unwarranted or are any potentially helpful limits missing?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

7. Adapted for db: Has the search strategy been adapted for each database to be searched?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

Other notes:

It is unclear how the tally of results adds together to a final n of 10709 as detailed in the flow diagram in section 5.2.2.

PRESS checklist- cost-effectiveness

1. Translation: Is the search question translated well into search concepts?

☑ Adequate

☐ Needs revision - Provide an explanation or example

_____

_____

2. Operators: Are there any mistakes in the use of Boolean or proximity operators?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

3. Subject headings: Are any important subject headings missing or have any irrelevant ones been included?

☑ Adequate, *but see note below*

☐ Needs revision Provide an explanation or example

_____ *The Embase and Medline database searches were combined and subject headings for Embase were applied, some of these were not applicable in Medline but they should have mapped over OK.*_____

4. Natural language: Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation used optimally?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

5. Spelling & syntax: Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers?

☑ Adequate, *but see note below*

☐ Needs revision Provide an explanation or example

The search string numbering is correct for the search but the Cochrane search-string needs to be renumbered starting at 1 not 54 so that it reads correctly in the report

6. Limits: Do any of the limits used seem unwarranted or are any potentially helpful limits missing?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

7. Adapted for db: Has the search strategy been adapted for each database to be searched?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

Other notes:

It is stated that the SIGN Economic filter has been applied to the search strategy, however it is not copied exactly over into the search strategy and some lines have been added, this change has not been explained, however the search strategy has all the components to pick-up all relevant references in this area.

The number of results at each stage of search has not been provided, therefore we are unable to check whether the final number of results tallies with the flow chart provided in Figure 14

PRESS checklist- measurement and valuation of health-effects

1. Translation: Is the search question translated well into search concepts?

☑ Adequate

☐ Needs revision - Provide an explanation or example

_____

_____

2. Operators: Are there any mistakes in the use of Boolean or proximity operators?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

3. Subject headings: Are any important subject headings missing or have any irrelevant ones been included?

☑ Adequate, *but see note below*

☐ Needs revision Provide an explanation or example

_____ *No subject headings are used but a comprehensive set of free text terms will pick up all relevenat articles, this search strategy is based on the search strategy used for TA101.*___

4. Natural language: Are any natural language terms or spelling variants missing, or have any irrelevant ones been included? Is truncation used optimally?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

5. Spelling & syntax: Does the search strategy have any spelling mistakes, system syntax errors, or wrong line numbers?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

_____

6. Limits: Do any of the limits used seem unwarranted or are any potentially helpful limits missing?

☑ Adequate

☐ Needs revision Provide an explanation or example

_____

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7. Adapted for db: Has the search strategy been adapted for each database to be searched?

☑ Adequate

☐ Needs revision Provide an explanation or example

Other notes:

The number of results at each stage of search has not been provided, therefore we are unable to check whether the final number of results tallies with the flow chart provided in Figure 23.

Appendix 6 Implementation of Weibull distributions within electronic model

The Weibull curves are based upon the manufacturer responses to questions A9 and A10. This is implemented within the model by cutting and pasting the values into the following range of cells within the *Survival* worksheet. Only the first 90 values are reported here to enable a cross check, but the values relating to the full 174 cycles are changed within the model (Table 48).

Table 48. Weibull curves for OS and PFS

	OS		PFS				OS		PFS		
	AAP	PP	AAP	PP	MP		AAP	PP	AAP	PP	MP
Cycle	G9:G53	H9:H53	K9:K53	L9:L53	N9:N53	Cycle	G54:G98	H54:H98	K54:K98	L54:L98	N54:N98
0	1.000	1.000	1.000	1.000	1.000	45	0.191	0.112	0.059	0.004	0.004
1	0.992	0.986	0.958	0.926	0.926	46	0.181	0.105	0.055	0.004	0.004
2	0.979	0.965	0.912	0.847	0.847	47	0.172	0.099	0.051	0.003	0.003
3	0.963	0.941	0.866	0.769	0.769	48	0.163	0.092	0.048	0.003	0.003
4	0.945	0.915	0.821	0.696	0.696	49	0.155	0.086	0.045	0.002	0.002
5	0.926	0.888	0.778	0.628	0.628	50	0.147	0.081	0.042	0.002	0.002
6	0.906	0.859	0.735	0.566	0.566	51	0.139	0.076	0.039	0.002	0.002
7	0.884	0.830	0.695	0.508	0.508	52	0.132	0.071	0.036	0.002	0.002
8	0.862	0.801	0.656	0.455	0.455	53	0.125	0.066	0.034	0.001	0.001
9	0.840	0.771	0.618	0.407	0.407	54	0.118	0.062	0.031	0.001	0.001
10	0.817	0.742	0.583	0.364	0.364	55	0.112	0.058	0.029	0.001	0.001
11	0.794	0.713	0.549	0.325	0.325	56	0.106	0.054	0.027	0.001	0.001
12	0.770	0.684	0.517	0.289	0.289	57	0.100	0.050	0.025	0.001	0.001
13	0.747	0.655	0.486	0.258	0.258	58	0.094	0.047	0.024	0.001	0.001
14	0.723	0.628	0.458	0.229	0.229	59	0.089	0.044	0.022	0.001	0.001
15	0.700	0.600	0.430	0.203	0.203	60	0.084	0.041	0.021	0.001	0.001
16	0.677	0.573	0.404	0.181	0.181	61	0.079	0.038	0.019	0.000	0.000
17	0.654	0.547	0.380	0.160	0.160	62	0.075	0.035	0.018	0.000	0.000
18	0.631	0.522	0.357	0.142	0.142	63	0.071	0.033	0.017	0.000	0.000
19	0.609	0.497	0.335	0.125	0.125	64	0.067	0.031	0.015	0.000	0.000
20	0.587	0.474	0.314	0.111	0.111	65	0.063	0.028	0.014	0.000	0.000
21	0.565	0.451	0.295	0.098	0.098	66	0.059	0.026	0.013	0.000	0.000
22	0.544	0.428	0.276	0.087	0.087	67	0.056	0.025	0.012	0.000	0.000
23	0.523	0.407	0.259	0.076	0.076	68	0.052	0.023	0.012	0.000	0.000
24	0.503	0.386	0.243	0.067	0.067	69	0.049	0.021	0.011	0.000	0.000
25	0.483	0.366	0.227	0.059	0.059	70	0.046	0.020	0.010	0.000	0.000
26	0.463	0.347	0.213	0.052	0.052	71	0.044	0.018	0.009	0.000	0.000
27	0.444	0.329	0.200	0.046	0.046	72	0.041	0.017	0.009	0.000	0.000
28	0.426	0.311	0.187	0.041	0.041	73	0.038	0.016	0.008	0.000	0.000
29	0.408	0.295	0.175	0.036	0.036	74	0.036	0.015	0.007	0.000	0.000
30	0.391	0.278	0.164	0.031	0.031	75	0.034	0.014	0.007	0.000	0.000
31	0.374	0.263	0.153	0.028	0.028	76	0.032	0.013	0.006	0.000	0.000
32	0.358	0.248	0.143	0.024	0.024	77	0.030	0.012	0.006	0.000	0.000
33	0.342	0.234	0.134	0.021	0.021	78	0.028	0.011	0.006	0.000	0.000
34	0.326	0.221	0.125	0.019	0.019	79	0.026	0.010	0.005	0.000	0.000
35	0.312	0.208	0.117	0.016	0.016	80	0.025	0.009	0.005	0.000	0.000
36	0.297	0.196	0.109	0.014	0.014	81	0.023	0.009	0.004	0.000	0.000
37	0.284	0.185	0.102	0.013	0.013	82	0.022	0.008	0.004	0.000	0.000
38	0.270	0.174	0.095	0.011	0.011	83	0.020	0.007	0.004	0.000	0.000
39	0.258	0.164	0.089	0.010	0.010	84	0.019	0.007	0.004	0.000	0.000
40	0.245	0.154	0.083	0.008	0.008	85	0.018	0.006	0.003	0.000	0.000
41	0.234	0.145	0.078	0.007	0.007	86	0.017	0.006	0.003	0.000	0.000
42	0.222	0.136	0.073	0.006	0.006	87	0.016	0.005	0.003	0.000	0.000
43	0.211	0.128	0.068	0.006	0.006	88	0.015	0.005	0.003	0.000	0.000
44	0.201	0.120	0.063	0.005	0.005	89	0.014	0.005	0.002	0.000	0.000

Appendix 7 Comparison of constant hazard extrapolation with Weibull parametric fit for OS

The constant hazard (exponential) extrapolation needs to be tested against alternatives. In the case of the AAP arm when the constant hazard extrapolation is extended back to time zero (red dotted line) a curve is generated that is removed from the observed (KM) data. When this is compared with a Weibull fit the choice of the constant hazard extrapolation is not well supported (Figure 16).

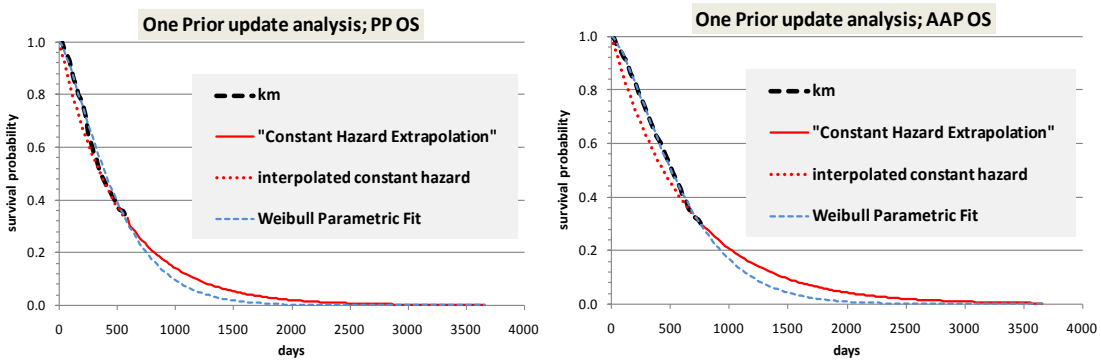

Figure 8. Back extension of the constant hazard extrapolation.
Manufacturer's base case compared with manufacturer's parametric fit to KM data.

For the comparator arm (PP) the backward extension of the constant hazard curve fits the KM observed data well and on the basis of visual inspection it is only slightly inferior to the Weibull parametric fit

The manufacturer's choice of a constant hazard extrapolation generates more life years gained from abiraterone over placebo than does the Weibull model (Figure 17).

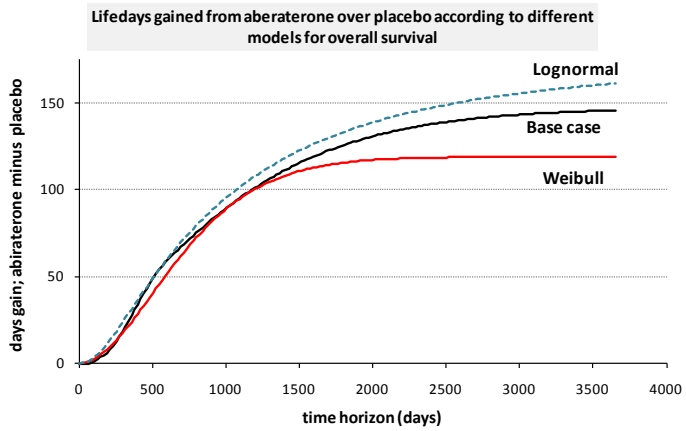

Figure 9. Cumulative gain in life days from abiraterone over placebo (no discounting)
Note: lognormal modelled gain is still rising after the 10 year time horizon