NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Abiraterone for treating metastatic hormone relapsed prostate cancer not previously treated with chemotherapy

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Janssen	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the appraisal consultation document (ACD). We are disappointed the Appraisal Committee's preliminary decision is that abiraterone is not recommended for patients with metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy; however, we are committed to working with NICE in order to address all of the Committee's key concerns outlined in the ACD.	Comment noted

Consultee	Comment	Response
Janssen	Our response addresses the following key issues: • **End of life (EoL) criteria**: The ACD states that the Committee did not consider the EoL criterion for short life expectancy (< 24 months) was met. We believe this criterion is in fact met because the published literature on survival estimates for this patient group consistently show that the life expectancy of this population is less than 24 months. • **Discrete event simulation (DES) model**: We are aware that the Committee has concerns over complexity and transparency of the DES model. We would like to clarify the steps taken when the model was constructed, and demonstrate that both the procedure followed and the outputs generated are robust. • **Survival benefit of abiraterone**: The Committee has concluded that the survival benefit of abiraterone was overestimated in the COU-AA-302 study. However, we believe that the benefit was robustly demonstrated in the trial, which has high internal validity. • **Early unblinding of the COU-AA-302 study**: The ACD notes that trial participants might regard early unblinding as unfair. Whilst ethical considerations surrounding randomised clinical trials are complex, we do not agree with this assertion as the unblinding decision was taken by the Independent Data Monitoring Committee, in keeping with standard practice in oncology trials. • **Benefits of delaying chemotherapy**: The ACD highlights that one of the benefits of abiraterone acetate is in delaying chemotherapy. Abiraterone offers significantly longer chemotherapy-free period for patients and their carers compared with current standard practice. It is important to recognise that such benefits cannot be readily captured in the standard cost per QALY framework.	Comments noted. Responses to these issues are given as they are described in more detail in subsequent sections.

Consultee	Comment	Response
Janssen	Abiraterone, discovered at the Institute of Cancer Research in London, is an example of a UK discovered innovation, and has quickly established itself as the standard of care in the post-docetaxel setting. Moreover, it is the first novel therapy to be licensed in the post-ADT, pre-chemotherapy setting, offering a step-change to those patients who have not received chemotherapy. The clinical demand for abiraterone in this setting is high as evidenced by the fact that it is the second most requested medicine on the Cancer Drugs Fund (CDF). We believe this response document addresses the key concerns raised in the ACD, and provides the relevant information for the Appraisal Committee to take into account in the forthcoming Committee meeting.	Comments noted. Section 4.25 of the FAD states that abiraterone is innovative. Section 4.1 notes that abiraterone for the pre-chemotherapy indication is currently available through the Cancer Drugs Fund.
Janssen	**2. End of life criteria** ***2.1 Short life expectancy, normally less than 24 months*** According to the ACD (para. 4.18), the Committee considered that the end-of-life (EoL) criterion for short life expectancy (< 24 months) was not met for abiraterone in the post-ADT, pre-chemotherapy setting. It appears that the Committee's view was predominantly related to the fact that there was an average of 30.1 months survival observed in the control arm of the COU-AA-302 trial. We believe it is important that the Committee recognises that the control arm of the clinical trial is not representative of average survival of metastatic prostate cancer patients in England and Wales and, as a result, should not be relied upon for determining whether EoL criteria are met. The COU-AA-302 study has high internal validity, which means that it is a robust source of evidence for estimating the effect size of benefit between the two treatment arms. However, Janssen believes that it is not appropriate to use the trial to estimate average absolute survival in UK patients in the absence of treatment is flawed for the following reasons:	Comments noted. The Committee's considerations of the company's concerns about whether COU-AA-302 is appropriate to estimate absolute survival in patients in English clinical practice are described in section 4.22 of the FAD. The Committee concluded that COU-AA-302 provides a reasonable estimate of the median life expectancy for people with metastatic hormone resistant prostate cancer for whom abiraterone is indicated, and that mean values generally exceed median values.
	• Firstly, this randomised controlled trial was carefully designed to assess the incremental clinical efficacy and safety of abiraterone compared to the control arm, but it is important to emphasise	Comments noted. Section 4.22 states

Consultee	Comment	Response
	that this study was not designed to answer questions related to the average survival of patients at this stage of their disease in the absence of the new treatment. Therefore, the committee needs to be cognisant of the limitations of using the data in this way to answer a question the study was never designed to answer. Patients enrolled in clinical trials are generally a fitter selection of the target population than those in real life clinical practice due to specific inclusion criteria. Of critical importance to this fact is that, in the COU-AA-302 trial, a specific inclusion criteria was that patients could only participate in the study if they were expected to have a life expectancy of at least 6 months. Patients who were at risk of dying within 6 months were therefore specifically excluded. This means that patients enrolled in the COU-AA-302 study would be, on average, expected to be fitter and thus have a longer survival compared with a general population of patients at this stage of the disease, as a specific subset of patients were pre-selected. Whilst randomisation enables the estimation of an effect size between treatments, this inclusion criteria has the impact of introducing an important element of bias, inflating the average survival estimate in the control arm upward.	that the Committee noted that COU-AA-302 excluded patients with significant comorbidities and a life expectancy of less than 6 months which would make life expectancy in the control arm longer than in the real-world population. However, the Committee noted that both the clinical specialists and the company had stated that COU-AA-302 was generalisable to clinical practice in England and reflected patients who would be offered abiraterone in England.
	• Secondly, this was an international study, and patients in the COU-AA-302 trial had significant exposure to other novel medications after the point of disease progression, which are not routinely available in the UK, and which would have the effect of extending survival over that which would be observed in usual practice (Table 1). Some of these medications, such as sipuleucel-T, cabazitaxel, ketoconazole and retreatment with abiraterone are not currently recommended by NICE and therefore do not align with current clinical practice in England and Wales. Of note, a higher proportion of patients received subsequent therapies in the control arm than in the abiraterone arm.	Comments noted. Section 4.21 of the FAD states the Committee concluded that the life expectancy of people in the best supportive care arm of COU-AA-302 reflected that of patients in the NHS because the subsequent active treatments in the best supportive care arm in

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td></td><td>COU-AA-302 were similar to those patients receive in routine clinical practice in the NHS.</td></tr>
<tr><td></td><td>

Table 1: Subsequent therapy for prostate cancer, COU-AA-302 study

<table>
<tr><th></th><th>Abiraterone plus prednisone (n=546), no. (%)</th><th>Prednisone alone (n=542), no. (%)</th></tr>
<tr><td>Patients with selected subsequent therapy for mCRPC</td><td>274 (50%)</td><td>348 (64%)</td></tr>
<tr><td>Docetaxel</td><td>239 (44%)</td><td>304 (56%)</td></tr>
<tr><td>Cabazitaxel</td><td>60 (11%)</td><td>70 (13%)</td></tr>
<tr><td>Ketoconazole</td><td>39 (7%)</td><td>63 (12%)</td></tr>
<tr><td>Abiraterone*</td><td>38 (7%)</td><td>78 (14%)</td></tr>
<tr><td>Sipuleucel-T</td><td>33 (6%)</td><td>28 (5%)</td></tr>
</table>

Note: Table reports cumulative incidence of subsequent therapy regardless of sequence after study drug discontinuation to the third interim analysis clinical cut-off date of 22 May 2012.
* Prior to unblinding and crossover from the prednisone arm to the abiraterone arm.

</td><td>Table noted.</td></tr>
</table>

Consultee	Comment	Response
Janssen	We have extensively reviewed the published literature on survival estimates for this patient group and we believe our analysis consistently demonstrates that the balance of evidence consistently supports our conclusion that the life expectancy of this population is less than 24 months, as summarised below: • The 2012-2014 European Association of Urology (EAU) guidelines state a mean survival of patients in this setting is between 9 and 27 months, depending upon the level of metastases. • The SWOG study shows that a PSA of ≤4 ng/mL after 7 months of ADT is a strong predictor of survival. In the COU-AA-302 study, the median PSA at baseline was approximately 10-fold higher; 40ng/ml. In the SWOG study, those patients with PSA >4ng/ml at the end of ADT demonstrated on average 13 months survival. Continued below.	Comments noted. Committees considerations of the company's review of the published literature are described in section 4.23 of the FAD. NICE notes that the estimate of 9-27 months comes from the 2012 guideline. NICE was unable to find reference to the cited data in the 2013/14 guidelines. Section 4.23 states [the Committee] had not been presented with evidence that the guidelines included a systematic review… the estimate from the 2012 European Association of Urology guideline had not been included in the 2013 and 2014 updates of this guideline instead, these updates referred to median survival estimates from the docetaxel trials and trials of other technologies such as cabazitaxel, enzalutamide, sipuleucel-T and abiraterone The primary finding from the observational analysis from a clinical trial of androgen deprivation therapy

Consultee	Comment	Response
	Continued • Lastly, a systematic literature review by Kirby et al. showed the median survival of patients with castrate-resistant prostate cancer (CRPC) to range between 9 to 30 months, with considerably shorter estimates for those with metastatic disease (9 to 13 months). A pooled sample-weighted survival estimate from populations included in the review was 14 months.	[The Committee] was unclear how generalisable the populations included in the systematic review of observational studies were to the population in England for whom abiraterone is indicated (FAD section 4.23)
Janssen	In making a balanced judgement about whether this EoL criterion is met, we believe that the Committee should fully acknowledge the limitations of relying on the control arm of the COU-AA-302 study and take close account of the consistent evidence we have outlined above. This evidence, from different sources, all support the case for accepting the plausibility that survival in this group of patients would on average be less than 24 months. Furthermore, this approach would be consistent with many other previous NICE TAs where the EoL criteria were considered. We reviewed both the NICE website and the HTAinSite database, searching all NICE TAs for which the EoL criteria were considered. This search, which was validated for accuracy by an independent consultancy (see Appendix 1), identified a total of 35 STAs and 4 MTAs. The source of evidence used to demonstrate a life expectancy of less than 24 months varied among TAs, with no single source of evidence being explicitly preferred by the Committee. In numerous cases, multiple sources were presented to support a life expectancy of less than 24 months. Whilst median OS from the control arm of the clinical trial(s) was a common source (n=27), published literature (including other published clinical trials in the disease area) (n=13) and expert clinical opinion were also used (n=6) (Table 2). This illustrates the importance of evaluating each appraisal on a case by case basis and recognising when the clinical trial may or may not be the best available evidence to assess suitability for EoL.	Comment noted. The company's comments have been considered by the Committee, and these considerations have been described in sections 4.21 to 4.23 of the FAD. Comments noted. The Appraisal Committee considers the best available evidence for each appraisal separately.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Janssen</td><td>

Table 2: EoL criterion of short life expectancy (<24 months) - Basis for decision making

<table>
<tr><th>Basis for decision making</th><th>No. of technologies</th></tr>
<tr><td>Control arm of clinical trial</td><td>27</td></tr>
<tr><td>Published literature</td><td>13</td></tr>
<tr><td>Clinical opinion</td><td>6</td></tr>
<tr><td>Model estimates</td><td>4</td></tr>
</table>

</td><td>Table noted.</td></tr>
<tr><td>Janssen</td><td>

2.2 Extension to life, normally of at least an additional 3 months, compared to current NHS treatment

The COU-AA-302 trial demonstrated that, at the third interim analysis (IA3) with 55% of OS events (425 of 773), the median OS is 5.2 months longer in the abiraterone arm than in the control arm. The *mean* OS from the IA3 would be misleading because 45% of OS events had not occurred and thus many patients were still alive, and thus the median OS offers a better estimate of abiraterone's survival benefit.
Based on the economic model, the mean modelled OS benefit of abiraterone compared with the control arm is 9.3 months, which we believe demonstrates a significant survival advantage in favour of abiraterone.
Both the trial and model results indicate that abiraterone meets the EoL criterion of extension to life of at least 3 months.
This is consistent with previous TAs: Our analysis shows that in a significant proportion of TAs (n=21), the median OS reported from the relevant clinical trial(s) was the primary source of evidence and, in a minority of TAs (n=9), the modelled mean OS was also cited as an additional information source (**Error! Reference source not found.**).

</td><td>Comments noted. Section 4.25 of the FAD states: The Committee referred to its previous conclusion that there is uncertainty about the survival benefit with abiraterone because the median of 5.2 months may overestimate the true treatment effect because it was stopped early, and that the modelled mean benefit of 7.44 months [calculated from life years gained in base case] was likely to overestimate the true value because of the choice of extrapolation curves. However the Committee agreed that it is likely that abiraterone when given before docetaxel leads to a life extension of 3 months.</td></tr>
</table>

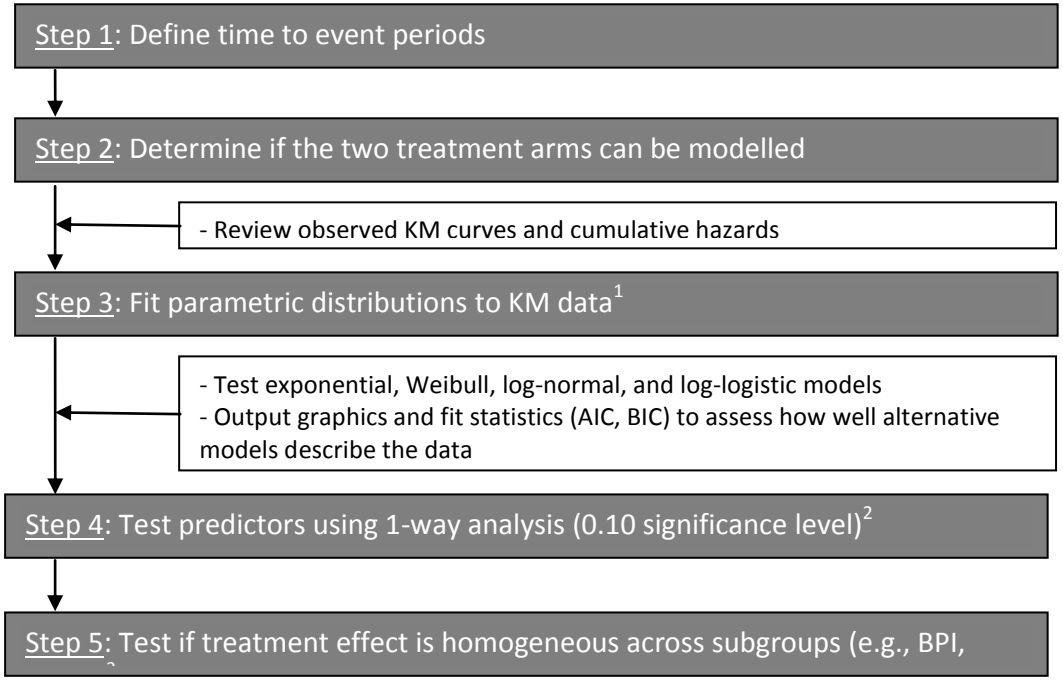
Consultee	Comment	Response
Janssen	***2.3 The treatment is licensed or otherwise indicated for small patient populations*** The ACD (para. 4.18) notes that we had presented an estimate of the population eligible for abiraterone in England and Wales, rather than that for England only. Table 3 displays the estimated split between England and Wales. **Table 3: Patients eligible for treatment with abiraterone in the pre- and post-docetaxel settings** [table below] These estimates indicate that the eligible patient population is small, whether it is for England only, or for England and Wales combined. Moreover, according to figures released by NHS England, 3,023 applications were received by the Cancer Drugs Fund regarding the use of abiraterone in the post-ADT, pre-chemotherapy setting between April 2013 and March 2014. This confirms that abiraterone is indeed being used in a small patient population in UK clinical practice.	Comments noted. Section 4.25 of the FAD states: [the Committee] noted that the company, in its response to the appraisal consultation document, estimated that 6732 people would be eligible for the pre- and post-docetaxel marketing authorisations in England, but that a proportion of people eligible for abiraterone after docetaxel would not receive abiraterone if they received it before docetaxel. The Committee concluded that the eligible population for England did not exceed 7000 and that abiraterone therefore met the end of life criterion for a small patient population.

	England and Wales	England	Wales
Population	56,784,200	53,698,373	3,085,827
Estimated number of mCRPC patients	11,085	10,483	602
Chemotherapy-naïve	60%	60%	60%
No. chemotherapy naïve	6,651	6,290	361
Asymptomatic or mildly symptomatic	70.5%	70.5%	70.5%
Eligible patient population (A)	**4,689**	**4,434**	**255**
Receive docetaxel	40%	40%	40%
No. receiving docetaxel	4,434	4,193	241
Assume 70% of these are eligible for AAP post-docetaxel	3,104	2,935	169
Eligible patients after the introduction of AAP in the post-ADT, pre-chemotherapy setting (B)	**2,483**	**2,348**	**135**
Total no. of patients eligible for AAP in both pre- and post-docetaxel settings (A+B)	**7,172**	**6,782**	**390**

AAP, abiraterone acetate plus prednisone/prednisolone; ADT, androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer.

Consultee	Comment	Response
Janssen	**3. Discrete event simulation model** ***3.1 Model design*** According to the ACD (para. 4.8), the "Committee agreed that using a discrete event simulation model was not unreasonable, but that the manufacturer's model was particularly complex". In its report, the ERG stated that a "less elaborate Markov model (using more health states than the regular three-state model) would have been as appropriate and would have allowed the ERG much more flexibility in performing additional analyses" (page 14). We believe that, for this particular appraisal, a Markov approach would not necessarily be simpler than the discrete event simulation (DES) model for the following reasons: • First, a patient's disease progression and treatment choice depends upon past experience and the specific time point at which they move to the next treatment phase. However, unlike the DES model, Markov models have no memory as noted in the technical support document (TSD) on patient-level simulation recently published by NICE DSU: "state-transition models often employ a Markovian assumption in which it is assumed that future events are independent of past events. This makes it difficult to model situations where the likelihood of future state transitions is dependent on the time since a previous transition (e.g. time on current treatment) or the history of previous events" • Second, for a Markov model to capture multiple lines of treatment and time dependent transition probabilities, it would have to be fairly complicated with a cohort in each cycle needing to be tracked separately, given the no memory limitation of the Markov approach. In contrast, the DES is more efficient as indicated by the NICE DSU: "An individual patient-level methodology is likely to provide a more efficient and parsimonious solution than trying to implement a cohort model in situations where there is substantial non-Markovian behaviour due to its ability to track individual patients and record their event history and use this to update their risk of future events".	Comments noted. NICE can only respond to comments on the ACD rather than the ERG report. Section 4.10 of the FAD reiterates the text in the ACD and states [The Committee] understood that the company had developed a discrete simulation model, rather than the more commonly used Markov model, because it allowed more flexibility to reflect a sequence of treatments, and to model response to treatments that depend on previous treatments. Section 4.10 further states: The Committee agreed that using a discrete event simulation model was not, unreasonable, but that the company's model was particularly complex.

Consultee	Comment	Response
Janssen	***3.2 Prediction equations*** The ACD states: “for each of the model’s 17 equations predicting time to events, the Committee noted that the manufacturer needed to make a large number of judgements when determining which variables to include in the prediction equations, which covariates to retain in the equations, and which parametric distribution to choose for extrapolation” (para. 4.8). The same paragraph also notes: “The manufacturer did not clearly pre-specify its approach to each of these judgements”. We would like to clarify the steps taken and the pre-specified statistical methodologies employed in order to derive the prediction equations. Prediction equations are required for the DES model in order to predict when each patient transitions from one phase to another. Patient characteristics are included in the prediction equations because the model simulates one patient at a time, and using his characteristics can help us better replicate what actually happened in the trial. The COU-AA-302 study data are used to link individual patient characteristics (e.g. treatment, current ECOG, baseline BMI) to an event time (e.g. treatment start) using standard statistical procedures outlined in Figure 1.	Comments and clarification noted. The sentence “The manufacturer did not clearly pre-specify its approach to each of these judgements” has been removed from the FAD.

Consultee	Comment	Response
Janssen	**Figure 1: Statistical procedure to develop time-to-event prediction equations**  Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BPI, Brief Pain Inventory score; ECOG, Eastern Cooperative Oncology Group performance status [1]The main goal of time to event equations was to closely predict the time to event outcomes for the overall population. [2]Note that adding predictors ensures that variability in the outcomes between patients in the trial is captured correctly, which is important in DES modelling. Also, if a specific distribution does not predict the outcome for the entire population well, adding predictors will not correct for that and therefore the current order of the steps to estimate and select predictors is the most logical. [3]Only BPI is significant in the time to discontinuation AAP phase post-ADT.	Clarification noted

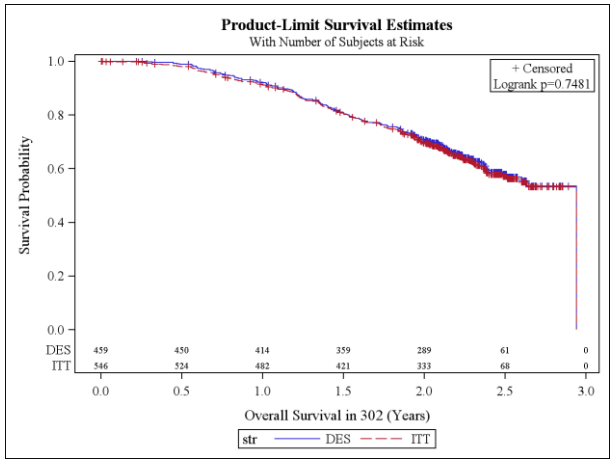
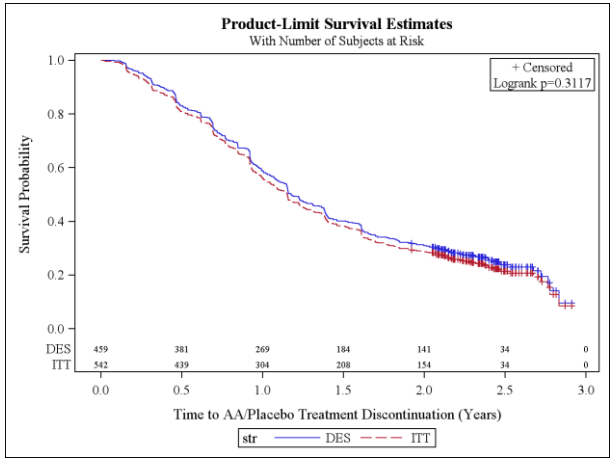
Consultee	Comment	Response
	The procedure illustrated above generated a series of prediction equations as shown in Table 4 and Table 5. **Table 4: Time-to-event prediction equations** From → To / Parametric distribution used AAP / WW(PP) start → AAP / WW(PP) end: Log-logistic AAP / WW(PP) end → Docetaxel start: Log-normal Docetaxel start → Docetaxel end: Weibull Docetaxel end → Post-docetaxel treatment start: Weibull Post-docetaxel treatment start → Post-docetaxel treatment end: Weibull AAP end → Death: Weibull WW (PP) end → Death: Weibull Docetaxel start → Death: Log-logistic Docetaxel end → Death: Weibull Post-docetaxel treatment end → Death: Weibull Abbreviations: AAP, abiraterone acetate plus prednisolone; BSC, best supportive care; PP, placebo plus prednisolone; WW, watchful waiting.	Table noted.

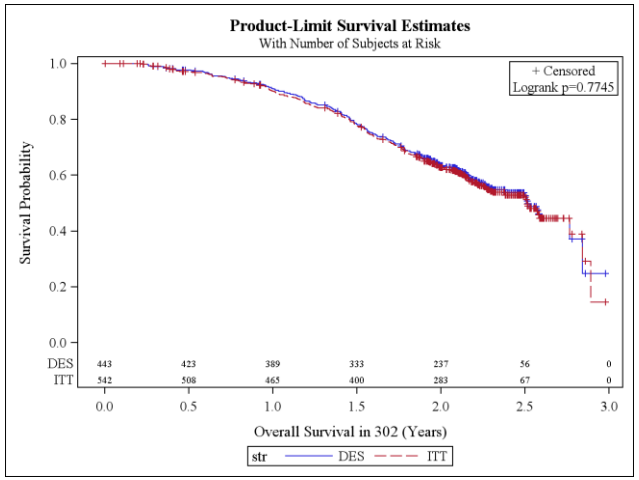
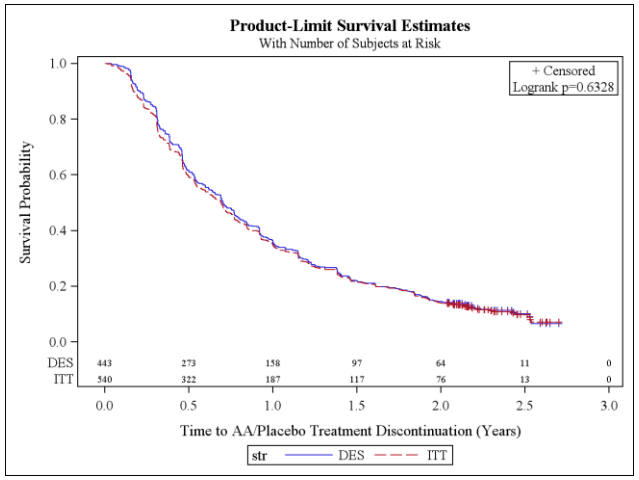
Consultee	Comment	Response
Janssen	**Table 5: Disease status prediction equations** ECOG status at AAP / WW(PP) end ECOG status at docetaxel start ECOG status at docetaxel end ECOG status at post-docetaxel treatment start PSA progression at AAP / WW (PP) end Radiographic progression at AAP / WW (PP) end Opiate use at AAP / WW (PP) end Abbreviations: AAP, abiraterone acetate plus prednisolone; ECOG, Eastern Cooperative Oncology Group; PP, placebo plus prednisolone; PSA, prostate-specific antigen; WW, watchful waiting. The ACD states: “the Committee appreciated that it is also important to take into account face validity and whether extrapolation predicts realistic outcomes, both for the event modelled by each equation, and for the model as a whole, but that this had not been done by the manufacturer” (para. 4.9). Janssen believes that this is not a fair conclusion because we followed a pre-defined protocol to assess the validity of the individual prediction equations (Figure 1). Also, comparisons between the fitted curves and the Kaplan-Meier curves from the trial have been previously provided to the ERG in our response to the clarification questions (see Figure 8 and Figures 10-28 in our response document). In summary, in order to derive the prediction equations, we performed necessary statistical analyses by diligently following the pre-defined procedure and by checking face validity of the final equations.	Table noted Comment noted. The text in 4.11 of the FAD has been amended to read: The Committee was aware that the company considered the Weibull, log-normal, log-logistic, exponential and gamma functions selecting the best fitting distribution using statistical criteria and inspecting the curves visually. However the Committee concluded that it is important to take into account face validity, and specifically whether extrapolating predicts realistic outcomes, both for the event modelled by each equation and the model as a whole, but that the company had not done this.

Consultee	Comment	Response
Janssen	***3.3 Analysable population vs. ITT population*** According to the ACD (para. 4.10), the "Committee was concerned that the selected group may not be representative of the ITT population, and of patients in England". When developing the prediction equations, the number of patients contributing to each equation depended upon which characteristics or predictors were retained in the final prediction equation. A total of 902 patients from the COU-AA-302 study had full baseline data (459 for AA and 443 for placebo) to inform the statistical analysis and to derive the prediction equations. The analysable dataset of 902 patients was also used to define the patient profiles in the model. We believe that missing of baseline information occurred completely at random and therefore does not bias the results. As Table 6 illustrates, baseline characteristics of the analysable population and the ITT population are very similar.	Comments noted. Section 4.12 of the FAD states: The Committee was aware that, in its response to the appraisal consultation document, the company presented the baseline characteristics for the subset of 902 people representing the modelled population, but that the company had not tested statistically whether this population differed from the ITT population.

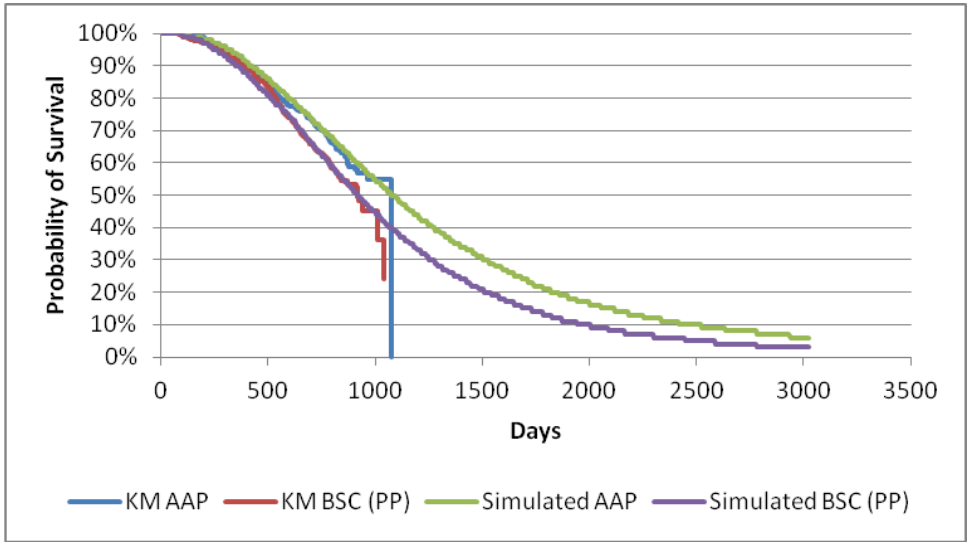
Consultee	Comment	Response
Janssen	**Table 6: Patient characteristics of analysable population vs. ITT population**	Table noted.

	ITT population		Analysable population	
Characteristic	**AAP (N=546)**	**PP (N=542)**	**AAP (N=459)**	**PP (N=443)**
Age, years, median	71	70	70	70
<65	24.7%	28.6%	25.3%	26.9%
65-69	20.5%	19.0%	21.4%	20.5%
70-74	20.9%	22.0%	20.9%	21.3%
≥75	33.9%	30.4%	32.5%	31.7%
Male, %	100	100	100	100
Race, %				
White	95.4	94.4	95.4	94.6
Black	2.8	2.4	2.6	2.5
Asian	0.7	1.7	0.9	1.6
Native Hawaiian / Other Pacific Islander	0	0.4	0.0	0.2
Other	1.1	1.1	1.1	1.1
Ethnicity, %				
Hispanic or Latino	4.6	4.5	3.7	4.8
Not Hispanic or Latino	95.4	95.5	96.3	95.2
Weight (kg), median	87.0	88.0	87.0	87.9
Height (cm), median	175.0	175.3	175.0	176.0
Mean time from diagnosis to first dose, years	6.7	6.5	6.79	6.5
Alkaline phosphatase, IU/L, median	93	90	93	90
Haemoglobin, g/dL, median)	13	13.1	13	13.1
Lactate dehydrogenase, IU/L, median	187	184	187	183
Baseline serum PSA, ng/mL				
Median	42	37.7	40.48	37.82
Range	0 – 3,927	1 – 6,606	0.04 – 3927.43	0.7 – 6606.44
BPI-SF #3 pain score, %				
0–1	68.6	64.8	74.07	69.75
2–3	23.9	27.5	25.93	30.25
≥4	7.4	7.7	0	0
Bone-only metastasis, %	50.4	49.3	51.85	50.11

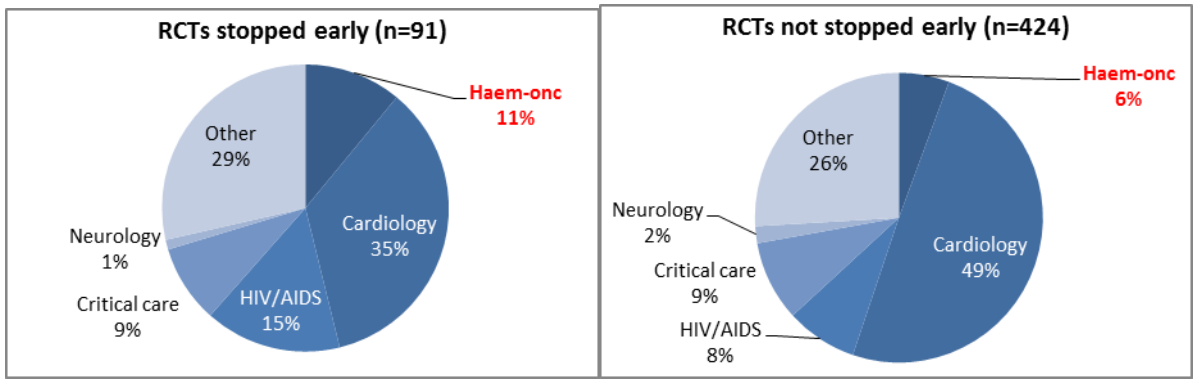
Consultee	Comment	Response
Janssen	As previously presented in our response to the ERG's clarification questions, Kaplan-Meier curves for both OS and time to treatment discontinuation (TTD) are very similar between the analysable and ITT populations (see Figure 2 to Figure 5). **Figure 2: Analysable vs. ITT populations – OS, abiraterone arm**  **Figure 3: Analysable vs. ITT populations – time to treatment discontinuation (TTD), abiraterone arm**  	Figures noted.

Consultee	Comment	Response
Janssen	**Figure 4: Analysable vs. ITT populations – OS, control arm**  **Figure 5: Analysable vs. ITT populations – time to treatment discontinuation (TTD), control arm**  	Figures noted.

Consultee	Comment	Response
Janssen	Comparisons between the analysable and ITT populations shown above illustrate that the two populations are indeed similar, and we believe that the ERG's concern ("the ITT population was not used (but a subset) and therefore the model results were probably not fully comparable with the ITT results of COU-AA-302" [para. 3.25]) are addressed by the results we present here.	Section 3.25 of the FAD reports the ERG review of the company's submission. No amendments are required to section 3.25
Janssen	The ACD also states that the Committee "noted the ERG's comments that using the subgroup favoured abiraterone compared with best supportive care because people in the subgroup were treated with abiraterone for longer than people in the ITT population, and this would have the effect in the model that overall survival improved" (para. 4.10). Again, this is not a relevant issue that impacts the cost-effectiveness of abiraterone for the following reason: • Contrary to the ERG's comment, the difference in TTD for abiraterone between two populations did not result in an overestimation of survival benefit of abiraterone over placebo. As Figure 6 illustrates, the model predicted the observed OS closely, particularly between year 1 and year 3 when most of treatment discontinuations occurred. This was also acknowledged in the ACD ("The Committee noted that the model results followed the trial results between day 540 and day 1080, at which point the trial data were unblinded." [para. 4.10]) Therefore, there is no evidence to suggest that the use of the analysable population, rather than the ITT population, favoured abiraterone compared against placebo. If anything, it may have resulted in a higher ICER than in a hypothetical situation where all relevant baseline characteristics were available for the overall ITT population. It is also important to note that small variation between the ITT trial survival curves and the modelled curves is partially attributable to the way the model accounts for subsequent novel therapies. In the trial, patients went on to receive subsequent treatments with interventions not available to UK patients (which occurred more in the control arm [Table 1]), and therefore the modelled curves are more likely to reflect the survival benefit that can be expected in the NHS.	Comments noted. The text "The Committee noted the ERG's comments that using the subgroup favoured abiraterone compared with best supportive care because people in the subgroup were treated with abiraterone for longer than people in the ITT population, and this would have the effect in the model that overall survival improved" has been removed from the FAD. Section 4.12 of the FAD describes the Committee's visual inspection of the trial data and the modelled data (company's figure 6 below).

Consultee	Comment	Response
Janssen	**Figure 6: Overall survival - observations from COU-AA-302 trial vs. predictions from the economic model**  	Figure noted. This figure was presented to Committee in the company's submission.

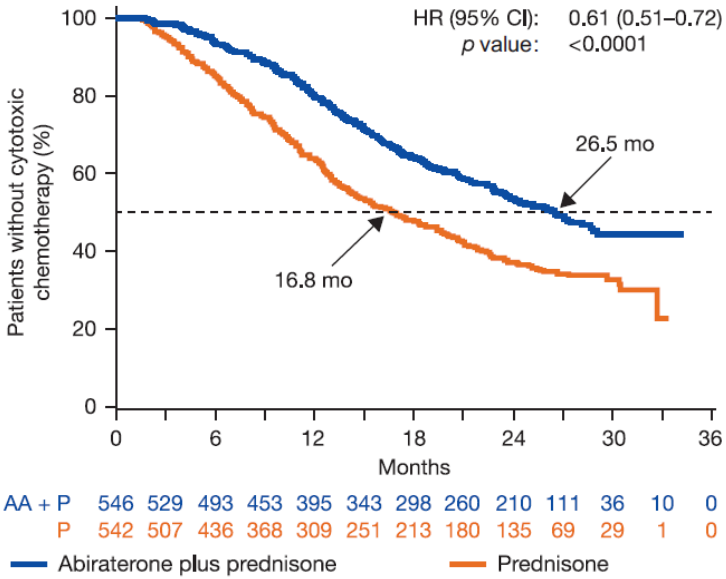
Consultee	Comment	Response
Janssen	**4. Survival benefit of abiraterone** The ACD states that “the Committee concluded that it was likely that the treatment effect of abiraterone on survival was overestimated” (para. 4.5). It appears that this assertion was based on a verbal comment made by a committee member who was referring to a single systematic review conducted by Bassler et al. We are surprised that this anecdotal comment, which if it were true would equally apply to many other appraisals, appears to have been used as a justification for questioning the robustness of the survival estimate. We have extensively reviewed this systematic review and are confident that it does not provide any robust justification for the Committee to conclude that the survival benefit of abiraterone is overestimated. Firstly, in their publication, Bassler et al. did not state that “trials that stop early show a larger treatment effect than trials that run to completion, and that trials stopped early because of benefit are likely to overestimate benefit by approximately 40%” (ACD para. 4.5). In fact, their key finding was that the pooled ratio of relative risks in truncated RCTs (i.e. those stopped early) vs. matching non-truncated RCTs was 0.71. This represents a 29% relative risk reduction, rather than 40%. Secondly, and of most relevance, the majority of RCTs reviewed by Bassler et al. were in cardiology and HIV/AIDS, and only a small minority (11%) was from haematology-oncology (Figure 7). Given that approximately 90% of the RCTs reviewed by Bassler et al. were from outside the haematology-oncology area, there is no clear relevance of these findings to this appraisal of patients with mCRPC.	Comment noted. Section 4.6 of the FAD includes the amended text: The Committee noted that a systematic review published in 2010 (Bassler et al.) describing the bias in trials that stop early for benefit. Specifically, compared with trials that run to completion, trials that stop early for benefit show a better effect of the treatment (that its, have pooled hazard ratios around 30% lower than trials that run to completion).

Consultee	Comment	Response
Janssen	**Figure 7: Disease areas of RCTs reviewed by Bassler et al.**  Indeed, Bassler et al. quoted reviews of oncology studies conducted by others: • "Korn and colleagues recently reviewed the results of cancer trials stopped early and that either continued with further follow-up or released results early. They found that substantial differences between results at the time of early stopping and subsequent follow-up seldom occurred." • "Freidlin and Korn published a related simulation study that supported these findings, suggesting that if the true effect is large, differences between stopped-early results and full follow-up results will differ little." These comments cast further doubts on whether the findings by Bassler et al. should be applied in the decision making process for this particular STA. Therefore, the basis for the Committee's conclusion regarding the survival benefit of abiraterone, namely the review paper by Bassler et al., does not appear to have relevance for the current decision problem. It is important to note that treatment with abiraterone resulted in a clinically meaningful improvement in OS. An estimated 21% decrease in the risk of death was observed (absolute risk reduction 6.6%), resulting in an additional 5.2 months of life. Although the result did not cross the boundary for statistical significance (p-value: observed 0.0151 vs. required 0.0034), this was due to the stringent pre-specified alpha-spending rules applied to the interim analyses. We believe that the survival benefit of abiraterone was clearly demonstrated in the COU-AA-302 trial, and there is no reason to believe that abiraterone's benefit was either over- or under-estimated.	Comment noted. Section 4.6 of the FAD has been updated to state: The company expressed its belief during consultation that because the review by Bassler et al included a minority of haematology/oncology trials, and because other studies indicate only a marginal bias towards overestimation in oncology trials that stopped early, this bias did not apply to oncology trials. However, the Committee concluded that this bias was unrelated to disease area. Comment noted. The company designed its own statistical plan and decided when to unblind COU-AA-302. No changes required.

Consultee	Comment	Response
Janssen	**5. Early unblinding of the COU-AA-302 study** The ACD states that the Committee "noted that people consented to participate in the study based on the original protocol, and they were not given the opportunity to consider this deviation from the protocol. The Committee considered that trial participants might regard this as unfair, undermining the value of the results, and reducing the value of their having taken part in the trial." We disagree with this assertion. Considered opinion on these matters is that it is unethical to knowingly harm patients by allowing those in the control arm to progress and die unnecessarily when sufficient evidence is available to determine whether or not there are substantial benefits of abiraterone compared with placebo. There was some criticism of Janssen at the committee meeting, where some individuals appeared to have the incorrect understanding that it was the company that took the decision to stop the trial early. This is wholly inaccurate. We want to re-emphasise that the decision to unblind the study was taken entirely independently of the company. Janssen had no part in that decision. Regulatory trials of cancer medicines (and other trials) mandate the creation of an independent data monitoring committee (IDMC) to oversee trial results at pre-specified time points to ensure that participants are treated ethically during a trial. One of the core roles of an IDMC is to recommend stopping trials early for three key reasons. Firstly, if safety concerns arise, stopping a trial ensures that participants are not unnecessarily exposed to an unproven treatment. Alternatively if the data demonstrates an overwhelming benefit for participants at an interim analysis point, the IDMC will recommend that the trial should be stopped, as it would be unethical to withhold an efficacious treatment from patients in the control arm. Lastly, a trial may be stopped early if the results in the control arm are identical to those in the experimental arm. A monitoring role is essential in these decisions. However, the company sponsoring the trial is blinded, so they cannot perform this service in order to mitigate any conflict of interest. In the case of the COU-AA-302, the IDMC was tasked to review the results and provide one of the following three recommendations at each of the analysis time points: • Recommend stopping study for safety reasons • Recommend study continues to next interim analysis on OS • Recommend stopping study for survival advantage and crossing over patients on the placebo arm	Comment noted. The following text has been removed from the FAD: "the Committee noted that people consented to participate in the study based on the original protocol, and they were not given the opportunity to consider this deviation from the protocol. The Committee considered that trial participants might regard this as unfair, undermining the value of the results and reducing the value of their having taken part in the trial." Comment noted. Based on the statement from the company at the second committee meeting section 4.6 of the FAD has been updated to read: the Committee heard from the company that, although there was not a statistically significant difference in overall survival between the treatment groups, the independent Data monitoring Committee

Consultee	Comment	Response
		had recommended stopping the trial (unblinding) based on the strength of the results for radiographic progression-free survival, which favoured abiraterone. It also heard that the company continued to collect observational data once the trial had been unblinded.
Janssen	The IDMC made a unanimous decision to stop COU-AA-302 at IA2 as all committee members felt the ethical thing to do was to stop the study in view of the highly significant advantage seen for survival among patients on Arm X which turned out to be the abiraterone arm. This decision was further supported by the high significance observed in the secondary endpoints the IDMC evaluated. No other questions or concerns were raised by committee members. The committee's recommendation to the study sponsors (Janssen/Cougar Biotechnology) was to stop the study and permit crossover from placebo to abiraterone, and to inform the regulatory authorities of this decision. Ethical considerations surrounding randomised clinical trials are indeed complex. However, the comment in the ACD (quoted above) is contrary to the generally accepted standard role of an IDMC, and also not plausible in the context of the COU-AA-302 study where it was clear that patients in the placebo arm would benefit from crossover to abiraterone.	Comments noted. The following text has been removed from the FAD: "the Committee noted that people consented to participate in the study based on the original protocol, and they were not given the opportunity to consider this deviation from the protocol. The Committee considered that trial participants might regard this as unfair, undermining the value of the results and reducing the value of their having taken part in the trial."

Consultee	Comment	Response
Janssen	**6. Benefits of delaying chemotherapy** An important benefit which was discussed by both the clinicians and patient groups during the Appraisal Committee meeting was the value of abiraterone in delaying or avoiding chemotherapy. This was mentioned numerous times in the ACD: • "The Committee heard from the clinical specialists that older people and people with comorbidities are less likely to be fit enough to have docetaxel, and that some patients chose not to have docetaxel." (para. 4.1) • "…clinicians would generally use [abiraterone], in addition to best supportive care, to treat people with few symptoms to delay chemotherapy, or to treat people who are unable or do not wish to have chemotherapy." (para. 4.1) • "The Committee heard from the patient experts about how important it is for patients to have the option of delaying chemotherapy. The patient experts explained that the adverse effects of chemotherapy are severe and may be particularly poorly tolerated by people who are older or who lack support from a partner or carer. The patient experts further stated that some people choose not to have cytotoxic chemotherapy to avoid the debilitating adverse effects and to maximise the quality of what remains of their lives, even if it may mean dying sooner. The Committee concluded that chemotherapy can reduce a person's quality of life and that treatments that delay the need for chemotherapy are highly valued by patients." (para. 4.2) • "The Committee noted the statements submitted by patient groups, which pointed out that patients usually can cope with the adverse effects of abiraterone that are usually mild and tolerable, particularly compared with those of docetaxel, and that one of the advantages of abiraterone is that it delays the debilitating effects of chemotherapy." (para. 4.6)	The company's summary of discussions on benefits of delaying chemotherapy included in the ACD is noted. The text in section 4.6 of the ACD has been updated as the points have been described elsewhere in the FAD. Section 4.7 of the FAD (describing adverse events associated with abiraterone) has been updated to read: The Committee noted that statements submitted by patient groups, which pointed out that patients usually find the adverse effects of abiraterone mild and tolerable. The Committee concluded that abiraterone increases the risk of adverse events compared with prednisolone alone, but that patients can tolerate adverse effects associated with abiraterone.

Consultee	Comment	Response
Janssen	Time to initiation of cytotoxic chemotherapy, one of the secondary endpoints in the COU-AA-302 trial, was nearly 10 months longer in the abiraterone arm than in the control arm (26.5 months vs. 16.8 month [Figure 8]). Abiraterone reduced the risk of chemotherapy initiation by 39% and the hazard ratio (0.61) was statistically significantly below one (p<0.0001). **Figure 8: Time to initiation of chemotherapy - COU-AA-302 [IA3]**  The trial results clearly demonstrate that, for those patients who eventually receive chemotherapy, abiraterone can allow them to stay chemotherapy-free significantly longer than under the current standard of care. Although docetaxel is recommended by NICE and widely used in today's UK clinical practice, it is associated with debilitating side effects and requires substantial emotional and physical support from nurses and carers. The impacts of cytotoxic therapy on a patient's body may not be confined to time on treatment, but could also stretch into the longer term for those that experience serious side effects.	Comment noted. These data were presented in the company's submission. No changes required.Section 4.26 of the FAD states: the Committee agreed that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling.

Consultee	Comment	Response
Janssen	There is also a group of patients who are unable to receive chemotherapy because they are not fit enough, or because they lack the social, family and emotional support that is necessary to cope with the rigors of chemotherapy with docetaxel. Indeed, as of IA3 of the COU-AA-302 study, a higher proportion of patients in the abiraterone arm still had not received docetaxel compared with the control arm (56% vs. 44%) (Table 1). With current NICE guidance, this group of men cannot access novel agents such as enzalutamide or abiraterone in the post-chemotherapy setting, which means that they are left without access to NICE approved options other than best supportive care. This creates a natural inequity in access for both clinical and social reasons, which approval of abiraterone in the post-ADT, pre-chemotherapy setting could redress.	Comment noted. Section 4.4 of the FAD states: [The Committee] understood that the company did not present a comparison of abiraterone with docetaxel, noting that the marketing authorisation is indicated for people for whom chemotherapy is not yet indicated. The Committee agreed this was appropriate. NICE cannot make recommendations for the use of abiraterone in people not fit for chemotherapy at the time chemotherapy is indicated because this is outside the licensed indication for abiraterone.

Consultee	Comment	Response
	Furthermore, whilst this benefit of abiraterone is highly relevant to the patient and their carers in this setting, it is not adequately captured within the cost per QALY evaluation: • The majority of patients who have metastatic prostate cancer are elderly, as the disease is most common in those over the age of 70. Many patients suffer co-morbidities, are likely to be reliant on family or carers and require emotional support to endure chemotherapy. Whilst abiraterone can delay or avoid the need for chemotherapy, such patient benefits cannot be adequately captured in the cost per QALY framework. • Many men at this age live alone, for example having been widowed. Such social isolation can be a barrier to receiving chemotherapy. Hence a patient's treatment pathway is determined not only by their health status, but is also highly dependent on social factors such as the support from nurses and carers, time spent with loved ones, practicalities of medical care and other day-to-day activities. Abiraterone's ability to alter the treatment pathway of this group of patients cannot be fully captured in the standard evaluation framework. • Metastatic prostate cancer can also occur in younger men who may also lack a stable support network, or may otherwise be the financial provider for a household. As a result, these men would require the necessary social support to help minimise the impact of time off work and travel expenses on their family whilst they undergo treatment. Again, the standard cost per QALY framework is not well suited to capture abiraterone's benefits for this group of patients. • Detrimental impact of chemotherapy on carers is well documented. For example, Turkoglu and Kılıc concluded that QoL of carers of cancer patients undergoing chemotherapy decline as carer burden increases. A recent UK study explored the needs of informal carers for patients having intravenous chemotherapy and illustrated different aspects of carer burdens. By delaying or avoiding the need for chemotherapy, abiraterone can benefit QoL of carers as well as that of patients. However, the standard cost per QALY framework does not adequately capture this benefit.	Comments noted. Section 4.26 of the FAD states: the Committee agreed that, the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. In its first meeting, the Committee considered that taking into account the benefits of delaying chemotherapy would be extremely unlikely to reduce the company's base case ICER for abiraterone to within the range usually considered a cost effective use of NHS resources The NICE reference case states that the perspective on outcomes is all direct health effects, whether for patients or, when relevant, carers.

Consultee	Comment	Response
	Extending the stage of disease when mCRPC is still asymptomatic or mildly symptomatic means patients may enjoy prolonged quality of life and more time with loved ones whilst their disease is less severe. Since abiraterone can be taken at home, there is minimal interruption to daily life and less need for frequent visits to hospital. Elderly patients in particular can therefore avoid the social anxiety associated with outpatient clinics and the financial requirements of travel. In addition, the value of delaying chemotherapy is felt indirectly by the family and carers of the patient as there is less demand for continuous physical, emotional and financial support required throughout chemotherapy. Indeed, such carer benefit appeals to a pivotal aspect of the NHS Outcomes Framework which recognises the vital role they play in supporting people who are ill and the importance of also maintaining their QoL (indicator 2.4 Health related quality of life for carers). As mentioned above, whilst many mCRPC patients are reliant on the care provided by others, some may not have a carer and hence would not cope with the arduous cycles of chemotherapy. These patients have no choice other than to receive best supportive care and would be excluded from receiving novel agents only available after chemotherapy. Elderly men are rarely naïve to their prognosis when diagnosed with metastatic prostate cancer, yet clinical opinion suggests that many would choose to avoid chemotherapy; Koedoot et al. found watchful waiting was preferred among cancer patients who expected severe toxicities from chemotherapy.	Comments noted. Please see responses above.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Janssen</td><td>

7. Other issues

7.1 Sensitivity analysis around the treatment effects

The ACD states: “The Committee further recognised that the manufacturer had not performed a sensitivity analysis around the treatment effect of abiraterone” and “key areas of uncertainty had not been explored” (para. 4.14).
To address this concern, additional sensitivity analyses have been performed by varying coefficients for treatment effects by one standard error in each direction. Table 7 indicates that varying treatment effect-related coefficients results in the ICER range between £41k/QALY to £55k/QALY.

Table 7: Results of the sensitivity analyses – treatment effects

<table>
<tr><th colspan="4">1) Treatment effect=mean – SE</th></tr>
<tr><th></th><th>AAP</th><th>PP</th><th>Incremental</th></tr>
<tr><td>LY</td><td>[redacted]</td><td>[redacted]</td><td>0.46</td></tr>
<tr><td>QALY</td><td>[redacted]</td><td>[redacted]</td><td>0.42</td></tr>
<tr><td>Cost</td><td>[redacted]</td><td>[redacted]</td><td>£23,136</td></tr>
<tr><td>Cost/QALY</td><td></td><td></td><td>£55,155</td></tr>
<tr><th colspan="4">2) Treatment effect=mean + SE</th></tr>
<tr><th></th><th>AAP</th><th>PP</th><th>Incremental</th></tr>
<tr><td>LY</td><td>[redacted]</td><td>[redacted]</td><td>0.81</td></tr>
<tr><td>QALY</td><td>[redacted]</td><td>[redacted]</td><td>0.73</td></tr>
<tr><td>Cost</td><td>[redacted]</td><td>[redacted]</td><td>£29,996</td></tr>
<tr><td>Cost/QALY</td><td></td><td></td><td>£41,248</td></tr>
</table>

</td><td>Analyses noted. These analyses have been described in section 3.30 of the FAD. Section 4.15 of the FAD has been updated to state: the Committee also noted that, following consultation on the appraisal consultation document, the company presented a sensitivity analysis that lowered the treatment effect of abiraterone from COU-AA-302 by 1 standard error and this increased the ICER to £55,000 per QALY gained. The Committee concluded that the company’s estimate of cost effectiveness was sensitive to assumptions around treatment effect.</td></tr>
</table>

Consultee	Comment	Response
	7.2 Docetaxel drug cost Para. 4.13 of the ACD discusses the cost of docetaxel in the model, and notes that “the price used by the manufacturer in the model seemed high”. To test the sensitivity of the ICER estimate on docetaxel acquisition cost, an additional analysis was performed whereby docetaxel cost was reduced by 20%. As shown in Table 8, the ICER estimate in this sensitivity analysis (£46,998/QALY) is highly similar to the one from the base case (£46,722/QALY), suggesting the ICER is not particularly sensitive to the cost of docetaxel. **Table 8: Result of the sensitivity analysis – docetaxel cost** [redacted]	Analysis noted. This analysis has been described in section 3.31 of the FAD. Section 4.16 of the FAD has been updated to state: the Committee noted that the additional sensitivity analysis provided by the company in its response to the appraisal consultation document including the cost of docetaxel reduced by 20%, resulted in an ICER of £47,000 per QALY gained. Committee concluded that the price paid for docetaxel in England may be less than the value tested by the company, but that the ICER was relatively insensitive to changes in the cost of docetaxel.

	AAP	PP	Incremental
QALY	[redacted]	[redacted]	0.57
Cost	[redacted]	[redacted]	£26,560
Cost/QALY			£46,998

Consultee	Comment	Response
Janssen	**8. Conclusion** Appraised in 2012 under end of life criteria, abiraterone in the post-chemotherapy setting was only recommended for use on the NHS following considerable efforts and a patient access scheme by Janssen to make the medicine available to NICE. [redacted] In this current appraisal in the pre-chemotherapy setting, the Committee has made an initial decision to reject abiraterone as they believe it does not meet the EoL criteria in the same patient population earlier in the treatment pathway. We believe that the balance of evidence supports our arguments that abiraterone continues to meet these criteria at this stage in the patient pathway. Given that abiraterone has already been appraised under these criteria in an indication in which it is used in the same types of patients later on in the prostate cancer pathway, such a decision not to apply the criteria on this occasion could illustrate the arbitrary nature of how these criteria are applied. It is important to note that the current indication under appraisal offers a range of clinically important benefits for men at an earlier stage of their disease, at a similar cost-effectiveness to the indication previously approved. It also provides an option for men who cannot go through chemotherapy for clinical or social reasons, and delays the time to chemotherapy for those who can. These are critically important benefits, but ones which are not easy to capture in a traditional cost per QALY framework. We therefore believe that there are a range of important benefits that are strongly under-represented in the economic analysis as it stands. If approved in the pre-chemotherapy setting, patients will receive abiraterone prior, as opposed to after, chemotherapy, providing more equitable access to this NICE approved medicine in the same group of patients, earlier in the course of their disease. **Appendix 1: Review of previous NICE HTAs in oncology and reference list are not reproduced here**	Comments noted. Please see above responses.

Consultee	Comment	Response
British Uro-oncology Group	The British Uro-oncology Group (BUG) is greatly concerned by the NICE Appraisal Committee's preliminary recommendation that: *1.1 Abiraterone is not recommended within its marketing authorisation for treating metastatic hormone-relapsed prostate cancer in people who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated.* The British Uro-oncology Group urges NICE to reconsider its preliminary recommendations in this ACD, considering the following points: a)Abiraterone has been the second most prescribed drug on the Cancer Drugs' Fund, with 3,023 patients treated in this setting between April 2013 and March 2014 in England. Members of BUG who represent the majority of uro-oncologists in the UK believe strongly in the value of this technology for the treatment of metastatic hormone relapsed prostate cancer in terms of efficacy, tolerability and also in the significant delay for treatment with chemotherapy, where clinically indicated and/or based on patient preference. b)The ability to prescribe abiraterone in patients not previously treated with chemotherapy delays disease progression and provides patients with a better quality of life with less pain. The patient benefit is highly significant. It is hugely disappointing that NICE does not appreciate the benefit of abiraterone when evaluating the end of life criteria. The longest survival data we currently have in this patient population is for patients receiving abiraterone first line (and then subsequent lines of therapy as dictated clinically). Some of these patients don't go on to receive docetaxel through choice, decline in Performance Status or other parameters, or the availability of other therapies. Our aim is to maximise quality of life and its duration - which a sequence starting with abiraterone achieves, with the best data to date. The members of the British Uro-oncology Group have significant clinical experience in the use of abiraterone, acting in the best interests of their patients. It would appear that the preliminary decision here, based primarily around cost, does not properly consider the licensed indication and benefits of abiraterone pre-chemotherapy, for men and their families living with prostate cancer. Thank you for your time in reviewing our comments on the ACD.	Comment noted. The Committee agreed that abiraterone met 2 criteria for end of life (abiraterone leads to life extension of 3 months and it is indicated for a small patient population of less than 7000 people). However because the short (24 month) life expectancy criterion had not been met, the Committee concluded that the end-of-life criteria did not apply to abiraterone taken before docetaxel in the treatment pathway. It is the remit of the NICE technology appraisal programme to appraise the cost-effectiveness of technologies. In this appraisal the Committee concluded that: abiraterone was likely to be effective and increase quality of life but abiraterone could not be considered a cost-effective use of NHS resources (section 4.26 of the FAD)

Consultee	Comment	Response
Royal College of Physicians	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to produce responses to NICE oncology appraisals. We are grateful for the opportunity to respond to the consultation on the above ACD and would like to make the following comments. • To qualify under the end of life criteria, survival with best supportive care should be less than 24 months. While this was exceeded in the control arm of the Cougar study, many patients crossed over to chemotherapy or received other novel hormone agents. The prolonged survival seen in both arms of this trial reflects what can be achieved with the use of abiraterone and new agents. However, it does not reflect the results of withholding these agents in patients who will receive best supportive care only. • In previous randomised trials of chemotherapy vs best supportive care (ie mitoxantrone) in this group of patients, the survival was far shorter. For example, in the TAX 327 study (Tannock NEJM 2004), where docetaxol was compared to mitoxantrone the survival in both arms was less than 24 months (19 and 16 months respectively). • Whilst the RCR agrees with the assertion that patients receiving abiraterone after chemotherapy would fare no worse than those receiving pre-chemo abiraterone, the guidance seems to ignore the situation of patients where chemotherapy is inappropriate, for reasons of age, performance status or co-morbid conditions. • Under the proposed guidance, these patients will receive neither chemotherapy nor abiraterone at any stage before death, and survival beyond two years in this group of patients is extremely unlikely, based on current evidence. • We would therefore strongly recommend that the committee examine the results of these studies as a more appropriate 'best supportive care' cohort, rather than the Cougar 301/302 studies, which are contaminated with cross-over and novel hormone agents from a variety of sources.	Comments noted. Section 4.21 of the FAD has been updated to state: The Committee concluded that life expectancy of people in the best supportive care arm of COU-AA-302 was reflective of that of patients in the NHS because the subsequent active treatments in the best supportive care arm of COU-AA-302 are similar to those patients receive in routine clinical practice in the NHS. The Committee considered the estimates from Tannock NEJM 2004 in the second meeting. Section 4.23 of the FAD has been updated to state: the trial comparing docetaxel to mitoxantrone mainly included people at a later stage of treatment who would be expected to have a shorter life expectancy than people for whom abiraterone is considered in this appraisal. NICE cannot make recommendations on the use of abiraterone in people not fit for chemotherapy at the

Consultee	Comment	Response
Prostate Cancer UK	**Prostate Cancer UK's view on the draft decision** Prostate Cancer UK is very concerned that this decision, if confirmed, will have a detrimental effect on men with prostate cancer. We urge NICE and the pharmaceutical company Janssen to work together so that men can access abiraterone on the NHS in England and Wales. As reported in the ACD document, albeit not capturing fully the true value to men with prostate cancer, delaying the use of chemotherapy can mean men are not faced with severe side effects of chemotherapy and therefore experience improved quality of life that abiraterone can offer earlier on in their treatment. As demonstrated in a recent phase III trial[i] abiraterone was shown to increase the time before prostate cancer could be seen to progress in chemotherapy-naïve men with metastatic castration-resistant prostate cancer by an average of 8.2 months. It has also increased the time before men started to experience other symptoms such as pain and a decline in performance status.	Comments noted. The company has the opportunity to respond to the ACD.
Prostate Cancer UK	**Clinical practice** The use of abiraterone before chemotherapy has been approved for use on the Cancer Drugs Fund (CDF), but this is only a temporary measure and the CDF applies in England only. Between April 2013 and March 2014 abiraterone, for this indication, was the second most requested treatment with 3,023 notifications received[ii]. This means that abiraterone before chemotherapy is now part of standard practice in England; we do not believe the ACD reflects this. We have asked several clinicians about their current use of abiraterone for this indication, comments included: "We are routinely using abiraterone before chemotherapy. Almost all patients, without exception." Benefits of abiraterone before chemotherapy: "Fewer side effects. Easier for patients to receive. Easier for departments to administer." "It is possible to use abiraterone in patients who would not have been otherwise fit for chemotherapy because of age, comorbidity and patient preference not to have chemotherapy." Therefore it is essential that NICE approves its use in order for standardise access elsewhere.	Comments noted. NICE cannot make recommendations for the use of abiraterone in people not fit for chemotherapy when chemotherapy is indicated because this is outside the marketing authorisation of abiraterone.

Consultee	Comment	Response
Prostate Cancer UK	**Abiraterone pre-chemotherapy: what do men with prostate cancer say?** As the UK's leading prostate cancer charity, we are in a privileged position to be able to represent the views of men with prostate cancer. As highlighted in our earlier submission to NICE, we surveyed men with prostate cancer to find out their views on abiraterone before chemotherapy. Of the 40 people affected by prostate cancer who responded to our survey, 30 people believe it is 'very important' (29) or 'important' (1) for abiraterone before chemotherapy to become a treatment option available to all men for whom it is clinically appropriate. When asked about benefits of abiraterone before chemotherapy, 26 people said that it was important to extend life for as long as possible. 24 said that it improved long-term control of the disease. 21 said it could provide a better quality of life, including less pain. 11 said it provided another treatment option when other treatments have failed. 14 said that an advantage of abiraterone before chemotherapy is that it can be administered orally.	Comments noted.

Consultee	Comment	Response
Prostate Cancer UK	Quotes on advantages include: “The prolonged survival is key. My dad is 62 and has so much he wants to do with the time left - even if it is just a few months, it would make a huge difference and allow him to maintain activities that are so important to his identity and sense of self before having the much more disruptive chemotherapy.” “My dear Dad died in September 2013 and I had asked for him to be given abiraterone several months before but he was not given it. Had he been given it before chemotherapy I think my Dad would still be here and not have died an agonising death.” “Chemo would usually be thought of as a last resort due to its extensive side effects so an additional treatment that is effective before chemo would be a huge improvement in the very limited number of options available for metastatic disease.” Abiraterone can help improve outcomes for men with this type of prostate cancer by delaying chemotherapy treatment, which often has debilitating side effects. These can include: nausea and vomiting, temporary bone marrow problems, fatigue, hair loss, loss of appetite, bowel problems (such as diarrhoea) and numbness of the hands and feet. Since the ACD was published on NICE’s website, we have been asking people affected by prostate cancer to provide their views on the draft decision. Comments have included: “Abiraterone should definitely be an option for men who haven’t had chemotherapy. Every man is different but just look at my results [PSA went from 500 to 0.05] – it turbo charged the effects of treatment and it was really heartening to see my PSA levels dropping. As far as my experience has been concerned it’s ticked all the boxes.” “Sadly my dad was told that he was not suitable for chemotherapy, this then meant he was unable to have abiraterone. He passed away in October 2012. We must keep going to get this through, wouldn't want anyone else to be refused treatment.”	Comments noted.

Consultee	Comment	Response
Prostate Cancer UK	**Conclusion** Prostate Cancer UK believes that NICE's draft recommendation on abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy is unacceptable, as this will deny those men access to this vital treatment option, especially when it is becoming commonplace for men for whom hormone therapy is no longer effective.	Comment noted. The Committee's overall conclusion was that abiraterone was likely to be effective and increase quality of live but could not be considered a cost effective use of NHS resources (FAD section 4.26)

Consultee	Comment	Response
Tackle prostate cancer	**This is Tackles response to the draft ACD rejecting market authorisation of the above.** 1. Disappointment that in the interim ACD NICE has refused market approval for what could be a very effective pathway for treating men for whom chemotherapy is not appropriate. In younger men or men whose fitness permit them to tolerate Chemotherapy, Abiraterone could be next treatment in the pathway but remembering that many men for whom hormone treatment has failed they will possibly be quite advanced in age and have a poor fitness level and cannot tolerate even one cycle of the chemotherapy treatment. For them the much less toxic Abiraterone is ideal. • In the evaluation by the ERG of this treatment no attempt was made to include as a discrete group of men, ones described above. In the submission documents NICE asks the question whether there is group of patients for whom this treatment is particularly effective. Well here is one and they have been been ignored • It must be recognised also by NICE that in this instance one QALY doesn't fit all groups of patients	Comments noted. NICE cannot make recommendations for the use of abiraterone in people not fit for chemotherapy when chemotherapy is indicated as this is outside the marketing authorisation of abiraterone. However, in response to consultation comments the Committee considered the use of abiraterone in people not fit enough for chemotherapy at the time abiraterone is given. These discussions are described in section 4.9 of the FAD. It states: The Committee therefore considered that there was no clinical evidence available to allow it to appraise the cost effectiveness of abiraterone in this population. The Committee therefore was unable to make a separate recommendation for this group.

Consultee	Comment	Response
	1. There are some contradictions in the interim ACD that need to be resolved for the final release. One key issue is the when the trial was stopped early because the benefits of the Abiraterone arm were so significant that it would have been unethical to allow those on the control arm to continue with the placebo. Later in the ACD NICE comment there was no such benefit. • How can a trial be stopped early because the benefits being shown in the active arm we so proven that not only would it have been unethical to carry on with the control on placebos and yet NICE in its wisdom ignore the substantial benefits by not allowing market authorisation. Tackle's membership and patients in general with hormone relapsed prostate cancer be not allowed this pathway if the their clinician decides that chemotherapy is not for them. People in ivory towers making these decisions do not allow for the deterioration in the quality of life with something as toxic as chemotherapy. These patients are already suffering the effects of the disease and treatments they have been having and now because of this draft ACD be exposed to the toxicity of chemotherapy as their only option. Please NICE show some understanding and compassion.	Comment noted. The Independent Data Monitoring Committee recommended stopping the trial based on the basis of radiographic progression free survival (FAD section 4.6). However the Committee noted that there was not a statistically significant difference in overall survival at the time the trial was stopped (FAD section 4.6) NICE does not grant marketing authorisations rather it makes recommendations for cost-effective technologies to be made available to all patients in England. In this appraisal, the Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost effective use of NHS resources (section 4.26 of FAD)

Consultee	Comment	Response
Tackle prostate cancer	1. There were data modelling issues between the manufacturer and NICE that cast a shadow over the outcome. These need to be resolved to give a true picture of the benefit both in survival time and cost per quality of life year. • This was one of the most turgid days spent listening to the ERG reviewing the evidence and going into detail that was incomprehensible to even clinician consultees. The ERG are permitted to refuse/challenge modelling techniques employed by the manufacturer but there is no reciprocal arrangement for the manufacturer to do this to the ERG. This is not democratic and allows NICE to steamroller their modelling answers to provide the QALY. This not fair and in this case the argument that Markov was better suited to analysis than the more complex technique employed by Janssen was not proven. **Tackles Conclusion** NICE must reverse the decision of the draft ACD and permit clinicians the flexibility to decide which of the two options for treating hormone relapsed prostate cancer is best for the patients survival.	Comment noted. Comment noted. The company has the opportunity to highlight any factual inaccuracies in the ERG's report and these comments are considered by the Committee. Section 4.10 of the FAD states that The Committee agreed that using a discrete event simulation model was not unreasonable, but that the company's model was particularly complex. Comment noted.

Consultee	Comment	Response
British Association of Urological Nurses	We feel this recommendation is disappointing as it drastically reduces the choices available to men with metastatic hormone relapsed prostate cancer – particularly for those who are not clinically fit enough for or would choose not to have chemotherapy and potentially impacts on the Qof L at this time. In our experience, Abiraterone in this setting gives men choice of treatment options. As reported in the document, patients generally tolerate the side effects of Abiraterone well as it has significantly less side effects than chemotherapy and therefore maintains their quality of life, for many months or often longer. Some men do not choose to have chemotherapy, and some wish to delay having chemotherapy and the consequent side effects and frequent hospital visits for as long as possible. For these men, this recommendation leaves them with no choice or active treatments at this time: a situation that is psychologically distressing as well as potentially putting men into a position of feeling coerced into a treatment that is not acceptable to them. Given that these men would be able to access Abiraterone after chemotherapy, there is little point in restricting treatment choices as to whether or when this drug is used in their treatment pathway. We believe that this decision should be based on patient choice and clinical judgement according the individual patient's needs and circumstances.	Comments noted NICE technology appraisals make recommendations on the cost effectiveness of technologies. In this appraisal the Committee concluded: abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources (FAD section 4.26).
British Association of Urological Nurses	We are also disappointed that the manufacturers were unable to fully disclose their research findings for consideration in this appraisal.	Comments noted.

Comments received from commentators

Commentator	Comment	Response
The Institute of Cancer Research	The Institute of Cancer Research (ICR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for abiraterone in the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. We are one of the world's most influential cancer research institutes, and work in close partnership with The Royal Marsden NHS Foundation Trust as the largest comprehensive cancer centre in Europe. Abiraterone was discovered by the ICR in its laboratories, in what is now the Cancer Research UK Cancer Therapeutics Unit, and the ICR and The Royal Marsden carried out initial clinical development on the drug, as well as leading the UK arms of later-stage international clinical trials. Abiraterone is now used as standard treatment after chemotherapy and has extended the lives of thousands of men in the UK with advanced prostate cancer. We are very disappointed that NICE, in the ACD's draft recommendations, did not feel able to recommend use of abiraterone for men with prostate cancer who are yet to receive chemotherapy. We understand that NICE must take into account both the clinical and cost-effectiveness of a drug when conducting its appraisals. We have a number of comments on the ACD and we deal with these below.	Comments noted.

Commentator	Comment	Response
The Institute of Cancer Research	*Clinical effectiveness* We believe the evidence is clear that abiraterone is effective when given before chemotherapy and can give men many extra months free of disease. We felt it was important to respond to questions raised by the committee about the endpoint used in the phase III clinical trial, and about the effect of unblinding the trial early on estimates of abiraterone's effects. Some 1,088 patients with prostate cancer that no longer responded to standard hormone-suppressing drugs but who had not received chemotherapy took part in the trial. Patients taking abiraterone went an average of 16.5 months before tumour growth was detected by a CT or MRI scan – twice as long as the 8.3 months among men taking a placebo. The trial had two primary measures, radiographic progression free survival and overall survival. The trial was stopped on the recommendation of the Independent Data Monitoring Committee when radiographic free survival reached significance, since the results were so impressive that the committee felt all men in the study should have the option to receive abiraterone. The trial was therefore stopped before the data on overall survival reached significance.	Comments noted. Comments noted. Section 4.6 of the FAD states: The Committee heard from the company that, although there was not a statistically significant difference in overall survival between the treatment groups, the Independent Data Monitoring Committee had recommended stopping (unblinding) the trial based on the strength of the results for radiographic progression-free survival, which favoured abiraterone.

Commentator	Comment	Response
The Institute of Cancer Research	*Cost effectiveness* NICE appears to have made its decision on the basis of cost, and we recognise that it does have a responsibility to achieve cost-effectiveness for the NHS. It is disappointing that abiraterone was considered too expensive to be recommended before chemotherapy. We believe that it is crucial that the NHS, NICE and the manufacturer reach an accommodation acceptable to all parties to ensure that this drug is made available and that more patients can gain the benefit of abiraterone. The manufacturer's base-case incremental cost-effectiveness ratio (ICER) is estimated to be £46,700 per QALY, which would be inside NICE's cost limit when the end of life criteria are applied. NICE did not apply its end of life criteria in this appraisal, as men who have not yet received chemotherapy now live for longer than two years. Abiraterone has therefore in part been a victim of the success of prostate cancer medicine.	Comments noted.

Commentator	Comment	Response
The Institute of Cancer Research	*Additional value not taken into account in the economic modelling* Abiraterone is now used as standard treatment after chemotherapy and has extended the lives of thousands of men in the UK with advanced prostate cancer. It has much milder side-effects than conventional chemotherapy, and the added benefit that it can be taken by men in their own homes. We are very disappointed that abiraterone was not recommended in the ACD for men with prostate cancer who are yet to receive chemotherapy. This decision would deny many thousands of men the opportunity to access this drug earlier in their course of treatment. In addition to strongly supporting the availability of abiraterone for all hormone relapse prostate cancer patients before chemotherapy, we would like to highlight that there is a particular group of patients affected by this decision. Many men with prostate cancer are elderly and are not in the position to receive chemotherapy as they might not be fit enough or might be too old. These patients could still benefit from abiraterone but by restricting its use to those who have already received chemotherapy, a significant number of men could now miss out on abiraterone too. Options for treatment are limited in this population, and they may even qualify for consideration under 'end of life' criteria as expected survival without treatment with chemotherapy or abiraterone will be considerably less than that of those who go on to receive further treatment. As the committee points out in the consultation document, the additional benefit of delaying chemotherapy or providing treatment options for those who are unable to have chemotherapy was not captured in the economic models, and we feel that greater weight needs to be given to this in the committee's decision.	Comments noted Comment noted. NICE cannot make recommendations for the use of abiraterone in people who need chemotherapy but who are not fit enough to have it as this is outside of the marketing authorisation for abiraterone. The Committee discussed the use of abiraterone in people who did not yet need chemotherapy but who would be considered not fit for chemotherapy. The Committee considered that there was no clinical evidence to allow it to appraise the cost effectiveness of abiraterone in this population. The Committee therefore was unable to make a separate recommendation for this group (section 4.9 FAD). Section 4.26 of the FAD states: The Committee considered that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the company's base case ICER for abiraterone to within the range usually considered a cost effective use of NHS resources. The Committee's view was reinforced by additional analysis carried out by the ERG – see section 3.32 of the FAD

Commentator	Comment	Response
Sanofi	Please find below Sanofi's response to the Appraisal Consultation Document (ACD) for abiraterone. Our comments all relate to the question as to whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. **1: Positioning of abiraterone and value of delaying chemotherapy** The ACD notes that delaying the use of chemotherapy is perceived to be one of the major benefits of abiraterone (used prior to docetaxel). However, it is critically important that the potential disadvantages of delaying chemotherapy are also taken into account. If chemotherapy is delayed, patients may experience disease progression and worsening of performance status that may either make them ineligible for chemotherapy or mean that they are less able to tolerate the side effects of chemotherapy if they do receive it. In the abiraterone submission, patients in the abiraterone arm had shorter durations of docetaxel chemotherapy compared to the best supportive care arm (4.13 of the ACD). Docetaxel chemotherapy was unequivocally proven to prolong overall survival in TAX327 – delaying initiation of docetaxel may result in fewer patients receiving the full survival benefit of this drug (Tannock et al 2004, NEJM 351; pp1502 – 1512). This should be viewed in the context of the uncertainty over the overall survival estimates in COU-302. Patient choice is clearly very important and many patients may choose not to undergo chemotherapy, however it is critical that they are able to make an informed choice, and are aware that delaying chemotherapy may mean that they are unable to gain the full survival advantage from the sequence of treatments now available to treat metastatic hormone refractory prostate cancer. Indeed, new evidence suggests that earlier use of chemotherapy in *hormone-sensitive* disease is beneficial, with a 13.6 month survival advantage demonstrated for docetaxel plus androgen deprivation therapy versus androgen deprivation therapy alone (HR 0.61, 95% CI 0.47-0.80, *P*=0.0003 [Sweeney et al, CHAARTED trial, Abstract number LBA2, ASCO 2014]).	Comments noted and are discussed in section 4.3 of the FAD. It states: [the Committee] also noted comments from consultation suggesting that when delaying chemotherapy disease and performance status may worsen, and that this may lead to some people becoming unable to tolerate the side effects associated with chemotherapy or to gain the full survival advantage from the sequence now available. The Committee appreciated that abiraterone delayed the time to treatment with cytotoxic chemotherapy in COU-AA-302, and understood from abiraterone's marketing authorisation that patients on abiraterone switch to docetaxel when clinically indicated, such that chemotherapy is not delayed once needed. The Committee concluded that there is some uncertainty about the consequences of delaying chemotherapy, but accepted the view of patients that delaying chemotherapy is of value to them.

Commentator	Comment	Response
Sanofi	It is particularly important not to delay chemotherapy in patients with rapidly progressing disease – as noted in the ACD (section 4.1) clinical experts do not consider it appropriate to use abiraterone to delay chemotherapy in patients who have rapidly progressing disease and who are fit enough to receive chemotherapy. It is important to recognise that the licensed indication for abiraterone is for patients who have no or mild symptoms after androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated and that this indication does not cover the entire population of patients with hormone-refractory metastatic disease who have not received chemotherapy. Indeed, the COU-302 trial was conducted only in patients who were asymptomatic or mildly symptomatic, and also excluded patients with visceral metastases (typically associated with rapidly progressing disease).	Comments noted.
Sanofi	**2: Evidence for the impact of chemotherapy on Quality of Life** The ACD notes that “The Committee concluded that chemotherapy can reduce a person’s quality of life”. While chemotherapy is associated with adverse events that may impact on quality of life, it should be noted that in fact the TAX327 trial of docetaxel shows positive effects on quality of life, with a significantly higher proportion of patients recording a response (defined as a 16-point improvement from baseline in the Functional Assessment of Cancer Therapy–Prostate [FACT-P] score on two measurements obtained at least three weeks apart) with docetaxel compared with mitoxantrone, a treatment primarily used for its palliative benefits (22% with docetaxel every 3 weeks, 23% with weekly docetaxel versus 13% with mitoxantrone, p = 0.009, p = 0.005 [Tannock et al 2004, NEJM 351; pp1502 – 1512]). This evidence indicates that the disease control afforded by docetaxel translates to improved, rather than reduced, quality of life.	Comments noted.

Commentator	Comment	Response
Sanofi	**3: Availability of cabazitaxel in the UK** We agree with the Committee that it is inappropriate to “adjust” post-docetaxel survival estimates from COU302 to exclude the survival benefit associated with cabazitaxel, as this treatment is available on the NHS in England through the Cancer Drugs Fund.	Comment noted

Comments received from members of the public

Role*	Section	Comment	Response
Patient	1	Where chemotherapy is not likely to be effective due to the spread of prostate cancer throughout the skeleton and lymphatic system the only effective treatment is abiraterone. Â The clinician should therefore be able to continue treatment until it is appropriate to stop.	Comment noted. Recommendation 1.2 states that people currently receiving treatment initiated within the NHS with abiraterone that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
	2	The technology is very effective and is good value for money given that the Department of Health considers that the administration of the patient access scheme does not constitute an excessive administrative burden on the NHS.	Comment noted. An administrative burden refers to additional costs of making the drug available to people on top of the drug costs. In this appraisal the Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources (FAD section 4.26).

* When comments are submitted via the Institute’s web site, individuals are asked to identify their role by choosing from a list as follows: ‘patent’, ‘carer’, ‘general public’, ‘health professional (within NHS)’, ‘health professional (private sector)’, ‘healthcare industry (pharmaceutical)’, ‘healthcare industry’(other)’, ‘local government professional’ or, if none of these categories apply, ‘other’ with a separate box to enter a description.

Role*	Section	Comment	Response
	4	There are insufficient characters allowed to properly address all the issues raised. The main arguments used by the committee ignore the ethical decisions made during the trial. Surely it is unethical to continue giving the placebo when the benefits of Abiraterone were clearly indicated.	Comments noted. The following text has been removed from the FAD: “the Committee noted that people consented to participate in the study based on the original protocol, and they were not given the opportunity to consider this deviation from the protocol. The Committee considered that trial participants might regard this as unfair, undermining the value of the results, and reducing the value of their having taken part in the trial”.
	5	I don't have access to these tools and thus cannot comment.	Comment noted
	7	No Comment	Comment noted
	8	No Comment	Comment noted

Role*	Section	Comment	Response
Carer	1	Why Abiraterone Should Be Allowed My husband has advanced and aggressive prostate cancer and has received 8 months of abiraterone before being prescribed docetaxel chemotherapy. I speak from experience when I say: Abiraterone was a very effective drug and gave him a good quality of life with no side effects at all. At the age of 65, it did keep the PSA down for a significant length of time and it has given him further quality time with his family. He experienced none of the weariness and fatigue that he had with other medications for advanced prostate cancer. There was no evidence of toxicity outside the acceptable medical range. The use of abiraterone has delayed the use of doxetaxel chemotherapy and this medication has proved to be much harder to physically tolerate. In contrast, docetaxel chemotherapy has had a very significant impact on his quality of life. He is at a much higher risk of infection and clinicians have seriously considered if the chemotherapy should be delayed for him. During the last 18 weeks of chemotherapy he has probably felt himself for no more than 7 ? 14 days. Many days since starting docetaxel chemotherapy have been spent in the bedroom and he has not dressed himself or got out of bed. Abiraterone allowed my husband to live an independent life. Once that failed, the tumour in his spine progressed and he is now confined to a wheelchair and also has the debilitating effects of the chemotherapy treatment. My husband is fortunate enough to have me as to attend to his needs, whereas many men will be living on their own. They will require a health and social care attendant for many basic everyday functions. Not all men are able to be able to travel to a chemotherapy centre without due stress and many will require hospitalization during this time.	Comments noted. The Committee's discussion of the comments on the benefits of delaying chemotherapy is in sections 4.2, 4.3 and 4.26 of the FAD. Section 4.26 of the FAD states that the Committee agreed that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, and the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. The Committee considered that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the company's base-case ICER for abiraterone to within the range usually considered a cost effective use of NHS resources. The Committee's view was reinforced by additional analysis carried out by the ERG – see section 3.32 of the FAD. The Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources.

Role*	Section	Comment	Response
	1 continued	The psychological aspects of social withdrawal, isolation and depression of having cancer, together with the added burden of chemotherapy are real and not exaggerated. Some men are much older than my husband and would poorly tolerate chemotherapy. Society may consider them elderly but they could still benefit and thrive with abiraterone. Abiraterone as a drug able to be prescribed prior to chemotherapy gives clinicians a real choice to work in the best interests of their patient. Abiraterone can delay the use of chemotherapy and may in some cases allow chemotherapy to be avoided altogether. Abiraterone is now the 2nd most requested drug on the cancer drugs fund and it is now part of best practice."	Comments noted see response above.
Patient	1	I am not convinced that there is sufficient definitive clinical evidence to conclude that use of arbiraterone before chemotherapy will not have a potential benefit for men like me with advanced prostate cancer	Comment noted. The Committee's overall conclusions following the second meeting are stated in section 4.26 of the FAD: The Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources.

Role*	Section	Comment	Response
Public	1	I do not believe arbitrone shpuld only be given after chemotherapy. Arbitrone can delay the need for chemotherapy and in some cases chemotherapy is not needed. Being able to take a tablet rather than chemotherapy which can be very gruelling and effect you physically and mentally as it is draining, a tablet makes it easier, less uncomfortable, less gruelling. Another important reason is because you can go about things as normal as there arent as many side effects as you get with chemotherapy. Beong able to live a normal, full and active life is vital to those fighting prostate cancer. Please do not wait until men have had to endure something that could possibly have many physical side effects before giving them arbitrone. Please make arbitrone available before chemotherapy and allow these men to live a fuller life in the process.	Comments noted. The Committee's discussion of the comments on the benefits of delaying chemotherapy are in sections 4.2, 4.3 and 4.25 of the FAD. Section 4.26 of the FAD states: The Committee agreed that the model predicted that people in the abiraterone arm have more time with better utility before docetaxel than people on best supportive care, and that the benefit of delaying chemotherapy perceived by patients may not have been fully captured in the modelling. The Committee considered that taking into account the benefit of delaying chemotherapy would be extremely unlikely to reduce the company's base-case ICER for abiraterone to within the range usually considered a cost effective use of NHS resources. The Committee's view was reinforced by additional analysis carried out by the ERG – see section 3.32 of the FAD. The Committee concluded that abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources.
Public	8	"Please consider the patients and the effects it has on their family, my Dad has prostrate Cancer which at the minute is contained but if he was to need these drugs we would be devastated if he wasn't allowed them because of the price, thanks.	Comment noted. It is NICE's remit to make sure that cost effective drugs are made available to people in England, however in this case the Committee concluded abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources (section 4.26 of the FAD).
Patient	1	- Abiraterone pre-chemotherapy was approved for use of the Cancer Drugs Fund in January 2013. It has proved popular with clinicians and is now part of current clinical practice. Abiraterone before chemotherapy is now the 2nd most requested drug on the Can	Comment noted.

Role*	Section	Comment	Response
Patient	1	I am still working full time under the use of this treatment, so very effective in keeping me in the tax area and still a proven benefit to the community.	Comment noted.
	2	I am taking this treatment for more than 15 months, not having had Chemotherapy. Funded from Cancer fund, only major problem is hypertension.	Comment noted.
Patient	3	I cannot understand a lot of the technical detail so difficult to comment. I just know that this drug is a real breakthrough in the treatment on castrate resistant PCa and should be given to any man that could potentially benefit.	Comment noted. It is NICE's remit to make sure that cost effective drugs are made available to people in England, however in this case the Committee concluded abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources (section 4.26of the FAD).
	4	All the people who have used this on the trial are not necessarily representative of the large numbers of men who need this drug, so the conclusions are not valid.	Comments noted. The Committee have to make use of the best data available to them in order to make their recommendations.
Public	1	Very disappointed with this decision. Making abiraterone available to men who haven't had chemotherapy could allow thousands of men in England and Wales to enjoy the reduced side effects and improved quality of life that this important drug can offer earlier on in their treatment.	Comment noted.
Public	1	I lost my grandad through cancer, and my father has recently had his prostate removed, it seems to be very common in males, it would be nice to give men the extra time to spend with there family	Comment noted.

Role*	Section	Comment	Response
Public	1	"Abiraterone pre-chemotherapy was approved for use of the Cancer Drugs Fund in January 2013. It has proved popular with clinicians and is now part of current clinical practice. Abiraterone before chemotherapy is now the 2nd most requested drug requested on the Cancer Drugs Fund. Prescribing abiraterone pre chemotherapy enables men to delay and in some cases avoid chemotherapy. This means being able to take a tablet at home, rather than travel into hospital for a treatment with significant side effects. This is a vital drug which should be available to all men on the NHS. If you have received treatment with either abiraterone or chemotherapy, then please do share your experiences with NICE. It's incredibly important that they hear from people who are directly affected by this decision or concerned about it."	Comment noted.
Patient	1	Abiraterone pre-chemotherapy was approved for use of the Cancer Drugs	Comment noted.
Carer	1	"My lovely husband who was 80 last November, fit and healthy all his life, might still be with us for a bit longer if the Wales NHS had given him Abiraterone first instead of chemotherapy. Absolutely devastated, it's disgusting that they didn't! Please make it available in Wales as well as England."	Comment noted.
Patient	1	I have advanced metastatic prostate cancer and have been on Arbiraterone Acetate and Prednisalone since Jan 2014. My PSA has reduced to 0.5 and scan show that my cancer has shrunk. I continue to work full time and pay my National Insurance and 40% tax every month. How many more are there like me being able to continuing to make a valuable contribution to society?	Comment noted.

Role*	Section	Comment	Response
Public	3	It seems to me that if the drug can prolong just one mans life, then the cost should not be a factor. This drug should be widely available to all patients that require it. Cost should not be a factor in someone's health and future quality of life.	It is NICE's remit to make sure that cost effective drugs are made available to people in England, however in this case the Committee concluded abiraterone was likely to be effective and increase quality of life but could not be considered a cost-effective use of NHS resources.
Patient	1	"- Abiraterone pre-chemotherapy was approved for use of the Cancer Drugs Fund in January 2013. It has proved popular with clinicians and is now part of current clinical practice. Abiraterone before chemotherapy is now the 2nd most requested drug requested "	Comment noted.

[i] Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. Charles J. Ryan, et.al The New England Journal of Medicine Vol 368 No 2 January 2013.
[ii] Quarterly figures – including notifications and Individual Cancer Drug Fund Requests (ICDFRs). Report April 2013-March 2014. http://www.england.nhs.uk/ourwork/pe/cdf/