NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen

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.

Comments received from consultees

Consultee	Comment	Response
Janssen	**Has all of the relevant evidence been taken into account and are the summaries for clinical and cost-effectiveness reasonable interpretations of the evidence?** We have a number of comments relating to these aspects of the appraisal. Following agreement from NICE, Janssen are submitting new evidence to address some of the Committee's key concerns outlined in the ACD. In summary, the main points we would wish to draw to the attention of the Committee, and which we have provided additional evidence, are as follows. • The licensed indication for abiraterone acetate in metastatic castrate resistant prostate cancer (mCRPC) covers the same eligible population as cabazitaxel, which was considered to meet end of life criteria. We believe that evidence presented in this response demonstrates that all three end of life criteria are met. • The use of abiraterone acetate in the 'One Prior Chemotherapy' population is representative of those who will receive the treatment in UK clinical practice. In this response, we are pleased to have the opportunity to demonstrate with new analyses of the clinical trial that there is a sound, biologically plausible basis for the selection of this population, which demonstrates differential clinical and cost-effectiveness outcomes compared to the whole population. • The utilities applied in the pre-progression health states within the economic analysis have been derived from robust analyses and are aligned with those accepted in other Technology Appraisals for metastatic and advanced solid tumours. Whilst the choice of post-progression utility comes from a separate source the model is insensitive to a wide range of post-progression utility values. • The use of Kaplan-Meier data in this case is an appropriate approach to analysing the overall survival and progression free survival data. As no single approach appears to explain the data, the Kaplan Meier approach taken in our base case can be considered closer to what could be expected in England and Wales for this patient population, given the maturity and completeness of the data in the COU-AA-301 study. A detailed response to each of these points is provided [**Not shown here**].	**End of Life Criteria** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21). **One prior chemotherapy subgroup** The Committee heard that the manufacturer considered the number of prior chemotherapies sufficiently important as a prognostic factor (in that more than one chemotherapy would imply a later stage of disease, more previous adverse reactions and more treatment-resistant tumours) to include it as a stratification factor for randomisation.

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Janssen	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Janssen propose that the Committee consider the new evidence submitted within this response, which provides a more robust, detailed, evidence-based grounding for the Committee's decision making.	The Committee also heard from the manufacturer that the difference in relative median overall survival benefit for abiraterone between the one prior chemotherapy subgroup and the subgroup who received more than one prior chemotherapy was supported by results for progression-free survival and other related outcomes from the COU-AA-301 trial. The difference was also supported by overall survival results from published studies of other second-line treatments for castration-resistant metastatic prostate cancer. The Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease. Therefore, the Committee concluded that it was reasonable based on biological plausibility and the pre-specification of this group in the COU-AA-301 trial (as a stratification factor) to accept this patient subgroup and its associated effectiveness data as the base-case for the analysis (FAD section 4.7). **Health state utility values** The Committee was aware that the manufacturer had not provided EQ-5D values for health states obtained directly from patients, which would have been in line with the preferred methods recommended by NICE, but had derived utility values for the pre-progression state from an algorithm that mapped FACT-P scores to EQ-5D utility values from a separate cross-sectional dataset of patients with castration-resistant metastatic prostate cancer. The Committee also noted that this mapping algorithm produced utility values that differed according to treatment. The Committee was aware that patients contributing to the cross-sectional dataset may have differed from the population in the COU-AA-301 trial and from patients who might receive abiraterone in the UK. The Committee also heard from the manufacturer that its mapping algorithm had not been externally validated.

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		The Committee noted that the mapping algorithm resulted in pre-progression utility values which were similar to or higher than utility values observed in the age-matched general population. In the Committee's view this might not be reasonable because people with metastatic prostate cancer would be expected to have a poorer quality of life than people without prostate cancer. However, it heard from the manufacturer and consultees that, because patients in the COU-AA-301 trial had few comorbidities and had been fit enough to receive chemotherapy, it was not implausible that they would have a similar health-related quality of life to people of the same age in the general UK population. The Committee also noted that the utility values for the pre-progression state were slightly higher than those used in the ongoing technology appraisal of cabazitaxel for metastatic hormone-refractory prostate cancer (derived from interim analysis of a small study). The Committee acknowledged a sensitivity analysis from the manufacturer which showed that when a published utility value of 0.715 (from the UK subgroup of Sullivan et al. 2007) was assigned to the pre-progression state, the ICER increased to £51,110 per QALY gained for abiraterone compared with prednisolone. However, the Committee was aware that the utility value taken from Sullivan et al. was based on a small patient subgroup and that this study may have included patients at different stages of prostate cancer. Additionally, the Committee also heard from one clinical specialist that the estimated utility gain for abiraterone compared with prednisolone may have been underestimated and, as a result, the ICER may have been overestimated. The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available (FAD section 4.14).

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		The Committee acknowledged that although patients were considered to be in the pre-progression state for the purposes of the model, they already had metastatic disease and would be unlikely to have the decrease in utility modelled by the manufacturer when progressing further to the post-progression state (defined only by stopping treatment). However, the Committee noted that a patient's health related quality of life could be very poor in the last months of life and that the post-progression utility value should also reflect this. Additionally, the Committee heard from the manufacturer that the utility difference between the pre-progression and post-progression health states was within the range used in recent technology appraisals of treatments for metastatic and advanced solid tumours. The Committee noted that a smaller utility difference between the pre-progression and post-progression health states would increase the ICER. The Committee concluded that uncertainty remained about the true difference in utility values between the pre-progression and post-progression states in the economic model, but that no other robust utility values that correctly capture the changes in health related quality of life in progressed disease were currently available (FAD section 4.15). **<u>Modelling of overall and progression-free survival</u>** The Committee considered that the Kaplan–Meier survival curves specifically reflected the COU-AA-301 trial population and whether a well-fitting parametric distribution would be more applicable to all patients for whom abiraterone may be a potential therapy in clinical practice. The Committee noted that the 10% cut-off chosen by the manufacturer for overall survival produced a relatively favourable ICER compared with other possible cut-off points.

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		The Committee heard from the manufacturer that fitting a specific parametric distribution to the overall survival curve was not necessary because survival data in the COU-AA-301 trial were almost complete and because additional analyses suggested that no single parametric function provides a better fit to the data than others. The Committee accepted that it may have been more appropriate to use a well-fitting parametric curve to extrapolate overall survival, but was also sympathetic to the manufacturer's argument that it is appropriate to use the observed Kaplan–Meier data when trial data were almost complete (FAD section 4.11). The Committee accepted that, although it would have been more appropriate to use a well-fitting parametric curve to extrapolate progression-free survival, data for time to treatment discontinuation in the COU-AA-301 trial were virtually complete and thus the impact on the ICER of using alternative assumptions was minimal (FAD section 4.13).
British Association of Urological Surgeons	1. NICE has rejected the manufacturer's economic model based on statistical modelling of data which the ERG conceded is associated with considerable uncertainties. While the committee accepted that the economic model submitted by the manufacturer closely adhered to the NICE reference for economic analysis, they concluded that an alternative model suggested by the ERG would be better applicable despite these uncertainties. 2. The next key issue relates to the manufacturer's preferred population for its base case, comprising of people who had received one prior chemotherapy only. Urologists and Oncologists in the United Kingdom would argue that this assumption is correct and accurately reflects the population of CRPC. Currently patients in only very exceptional circumstances would receive more than one type of chemotherapy prior to being considered for Abiratarone therapy. We would therefore disagree with the Committee's assumption that it was not appropriate to restrict the population considered in the basic analysis to the sub group with one	**<u>One prior chemotherapy subgroup</u>** The Committee heard that the manufacturer considered the number of prior chemotherapies sufficiently important as a prognostic factor (in that more than one chemotherapy would imply a later stage of disease, more previous adverse reactions and more treatment-resistant tumours) to include it as a stratification factor for randomisation. The Committee also heard from the manufacturer that the difference in relative median overall survival benefit for abiraterone between the one prior chemotherapy subgroup and the subgroup who received more than one prior chemotherapy was supported by results for progression-free survival and other related outcomes from the COU-AA-301 trial. The difference was also supported by overall survival results from published studies of other second-line treatments for castration-resistant metastatic prostate cancer. The Committee

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	prior chemotherapy. In fact the Expert Review Group also agreed with this in their report. 3. The third point relates to end of life criteria. While the Committee agrees that the criteria related to short life expectancy and extension of life were met, they argued that Abiratarone was not licensed for a small population. The definition of what constitutes a small population are obviously very variable and contentious and clinicians on the ground dealing with these patients would argue that the improvement in overall survival in patients with a limited life expectancy, should be the overall guiding principle. Survival improvements of this magnitude in this population of patients are unprecedented and therefore arguing on hypothetical grounds about relatively small numbers of patients and costs are not relevant. 4. I was personally disappointed to see that the Committee took into account factors in relation to the patient access scheme (PPRS). While the drug is available to patients currently in England via the patient access scheme, it is not available to patients in Scotland and has recently been approved by the AWMSG for use in Wales. In my opinion this should have no bearing on the Committee's decision as to whether this drug should be approved or not, and again raises the issue of post code prescribing with geographical variations in access to these treatments. 5. It is disappointing that both Abiratarone Acetate and Cabazitaxel have been rejected in recent weeks, despite them both being able to offer patients with castrate-resistant prostate cancer improvement of overall survival. This therefore limits patient choice and limits physicians' choice to offer the best available treatments.	accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease. Therefore, the Committee concluded that it was reasonable based on biological plausibility and the pre-specification of this group in the COU-AA-301 trial (as a stratification factor) to accept this patient subgroup and its associated effectiveness data as the base-case for the analysis (FAD section 4.7). **End of Life Criteria** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).

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		Patient Access Scheme The manufacturer has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published (FAD section 2.3). It should be noted that NICE guidance on abiraterone for the treatment of castration-resistant metastatic prostate cancer will be applicable to patients in England and Wales. **Final draft guidance** The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
British Uro-Oncology Group	The criteria used by the NICE Committee to reject abiraterone have been questioned by some BUG members and the recommendations have been criticised on the basis of some of the conclusions drawn. The Committee agreed that the criteria related to short life expectancy (less than 24 months) without treatment and extension to life (at least 3 months) with treatment were met. However, the Committee concluded that ***abiraterone was not licensed for a small population***, and therefore considered that it does not meet the criteria for an end-of-life treatment.' We are unable to find a definition of 'small population' and it seems unreasonable that a treatment of comparative cost-effectiveness is approved simply because it is for patients with rarer cancers.' There were several other comments that the population described by NICE who would be eligible for the drug was higher than that anticipated in clinical practice. The view of responding oncologists were that this was more likely to be approximately	**End of Life Criteria** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation

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	between 3,000 to 4,000 which could make a difference to the conclusion that abiraterone did not meet end of life criteria. There were also comments regarding the membership of the NICE Committee: 'It is disappointing that the Appraisal Committee did not involve an oncologist, and consequently, it is not clear that the potential 'cost-benefits' of this novel treatment, with a very favourable side-effect profile, have been appropriately acknowledged and considered. Accordingly, it is worthwhile noting a comment in the submission from NCRI/RCP/RCR/ACP/JCCO: 'Abiraterone not only improves survival, but also very effectively controls symptoms and reduces skeletal related events. We believe it will reduce the resources required to look after these patients because of better symptom control'. The data provided by the commissioning expert state that 20-30% of patients with progressive prostate cancer post docetaxel chemotherapy are treated with mitoxantrone. This is not thought to be a reasonable alternative to abiraterone due to the fact that there is no known data for survival advantage with this chemotherapy regimen and there is considerable toxicity. The cost of any new drug is of course important and as oncologists we acknowledge that we have a responsibility to prescribe any compound appropriately within its licence and only for the duration of response to therapy. There have been comments that it would be important to have defined end points as to when to withdraw abiraterone therapy. We concur with the opinion of the clinical specialists present at the review that it is very unlikely that abiraterone will be administered to men with an ECOG performance status of 2 and this is verified by the patients entered into the COU-AA-301 study where the minority of patients randomised (10%) were of this performance status. The inclusion and exclusion criteria used in the study are applicable and in keeping with routine clinical practice in the UK and those patients considered for abiraterone would be a similar population to those in the study. This is not consistent with the statement made by the NICE Appraisal Committee that patients treated in routine practice would be fitter than those in the study. The NICE appraisal committee's rejection on the quality of life data for abiraterone has also been a cause for comment and some variation in opinion. It was accepted that health economic modelling is difficult to unravel and messy. We received the following comments: 'The randomised trial measured	document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21). The Committee heard from clinical specialists that participants in the COU-AA-301 trial were likely to be healthier than those who would receive abiraterone treatment in UK clinical practice. However, it acknowledged that, in response to the appraisal consultation document, a number of comments from clinical organisations suggested that participants in the COU-AA-301 trial would be similar to patients who would be considered for abiraterone treatment in UK clinical practice (FAD section 4.4). **Health state utility values** The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available (see FAD section 4.14) and that uncertainty remained about the true difference in utility values between the pre-progression and post-progression states in the economic model, but that no other robust utility values that correctly capture the changes in health related quality of life in progressed disease were currently available (see FAD section 4.15). **Final draft guidance** The final draft guidance recommends the use of

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	quality of life using a different instrument to that required by NICE. It also stopped measuring quality of life on treatment discontinuation so a uniform health utility value (derived from a Swedish study) was applied after that. It might be the case that the abiraterone patients had a different clinical course from the control arm after treatment discontinuation. The conversion of the trial quality of life measurements to the EQ-5D measure required by NICE adds more uncertainty. The quality of life and health utility values have not been adequately measured in the study and consequently the health economic modelling is full of uncertainties. One BUG member stated that 'NICE has no choice but to make it assessment based on the poor quality cost-effectiveness evidence provided (even though the clinical effectiveness is beyond doubt). In the absence of robust cost-effectiveness data the only conclusion one can draw from this is that abiraterone is too expensive.' There were other opinions that FACT-P is a reasonable quality of life measurement and accepted by many other authorities including the FDA. It is impossible to satisfy the demands of everyone in an International multi-centre study. The criticism by the NICE Appraisal Committee that quality of life was not recorded in the post progression state seems to be unfair as this is not an unusual situation in many similar studies investigating drugs in the end of life criteria. These statements should not detract from the strong evidence that the quality of life was strongly positive during treatment. Abiraterone has a clinical advantage with a significant overall survival benefit and improvements in pain scores and reduced skeletal events. There has been considerable strength of opinion from UK oncologists that abiraterone is without doubt a very beneficial end of life drug which has shown good efficacy with minimal toxicity. It is felt that it should be considered by NICE to fulfil the criteria to be considered in this category. Members of BUG have expressed disappointment and concerns that men with metastatic castration resistant prostate cancer may be denied an effective 2nd line agent that not only significantly improves life expectancy, but also quality of life during treatment if the NICE Committee does not reconsider their ruling for abiraterone.	abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Cancer Research	**Are the summaries of clinical and cost effectiveness reasonable**	The Committee noted that the mapping algorithm resulted

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UK	**interpretations of the evidence?** There is agreement that is an effective, safe and well tolerated drug that prolongs life and improves quality of life. There is disagreement between the company and the ERG on the precise details of cost effectiveness modeling and assignation of health Utility Values, but this is beyond the scope of our professional expertise. We have concerns that the ERG assumes that men who may be offered treatment with Abiraterone have a low Utility Value, but it we would like to point out that these men generally have few co-morbidities otherwise they would not have been fit enough for the previous docetaxel and reduced functionality is generally due solely to their cancer. As a group, they are fitter than average for their years in our judgement. Abiraterone clearly leads to an improvement in quality of life and pain scores in men with symptoms and delays onset of pain in asymptomatic men.	in pre-progression utility values which were similar to or higher than utility values observed in the age-matched general population. In the Committee's view this might not be reasonable because people with metastatic prostate cancer would be expected to have a poorer quality of life than people without prostate cancer. However, it heard from the manufacturer and consultees that, because patients in the COU-AA-301 trial had few comorbidities and had been fit enough to receive chemotherapy, it was not implausible that they would have a similar health-related quality of life to people of the same age in the general UK population. The Committee also noted that the utility values for the pre-progression state were slightly higher than those used in the ongoing technology appraisal of cabazitaxel for metastatic hormone-refractory prostate cancer (derived from interim analysis of a small study). The Committee acknowledged a sensitivity analysis from the manufacturer which showed that when a published utility value of 0.715 (from the UK subgroup of Sullivan et al. 2007) was assigned to the pre-progression state, the ICER increased to £51,110 per QALY gained for abiraterone compared with prednisolone. However, the Committee was aware that the utility value taken from Sullivan et al. was based on a small patient subgroup and that this study may have included patients at different stages of prostate cancer. Additionally, the Committee also heard from one clinical specialist that the estimated utility gain for abiraterone compared with prednisolone may have been underestimated and, as a result, the ICER may have been overestimated. The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available (FAD section 4.14).

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	The steep fall off in the trial was a real event and we think it may represent the ability of the trialists to keep to the protocol and maintain patients on drug/placebo even though they were progressing clinically and biochemically. At 3 months radiological confirmation of disease progression would have resulted in a large number of patients coming off drug (placebo) at the same time point. We think that this means patients are modelled to stay in the pre-progression state for longer in the prednisolone arm than happened in the trial and thus underestimated the real benefit of Abiraterone. We believe that Abiraterone is an innovative drug as it is the first in class of a biologically targeted agent aimed at inhibiting a key pathway in androgen biosynthesis. Studies with this agent have shown that prostate cancers, far from becoming 'hormone-resistant', remain androgen –driven and indeed are androgen super-sensitive, in that they synthesise and respond to low levels of their own androgen. Abiraterone is the drug that has led to a redefinition of the disease states in prostate cancer (though our Consumer representatives have consistently reminded us that patients do not like the term 'castrate-resistant'). Another economic consequence of this appraisal would be that UK participation in future international cancer trials is significantly reduced, as NHS standard practice is significantly different from the rest of the international community. The patient representatives on the CSG feel particularly strongly about this, as an important issue additional to the concerns about the availability of the drug to suitable patients. For patients whose treatment would have otherwise been funded in a trials setting, the full costs will now fall on the NHS. This deserves to be modelled. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No We believe that this drug should be considered under the 'end of life' considerations at it meets <u>all</u> of the requirements, specifically that previous agreed end of life diseases have included a patient population of over 5000, and the total population of patients with prostate cancer who are fit enough to receive docetaxel falls well short of the approximately 10-12,000 who die of prostate cancer per year in the UK – in some regions it may be as few as 20%. We accept that there may remain some doubt about the ICER. However, we believe that NICE and Janssen should consider innovative approaches to ensuring patient access to Abiraterone while the uncertainties re ICER are addressed.	The Committee considered that abiraterone may offer a step change in treatment because it is life-extending rather than only palliative but that this element of innovation would already be accounted for when moving from an ICER of £20,000 to £30,000 per QALY gained. The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions. The benefit related to being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. The Committee therefore acknowledged that abiraterone provides health-related quality of life benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone, and that the ICER would decrease when these benefits were taken into consideration (FAD section 4.19). The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).

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Prostate Cancer Support Federation	On behalf of the Prostate Cancer Support Federation, I am writing to express my dismay about the decision by NICE to refuse Abiraterone for men with failed chemotherapy for prostate cancer. Having personal experience of this drug, I can testify to its very positive effect. When my chemotherapy failed in June 2011, my psa was 0.4. It began doubling every month and I was getting pain in my pelvic area and in my legs. On December 13th 2011, it stood at 25.6 and I realised I was in trouble. After just four weeks on Abiraterone, on January 13th 2012, my psa had dropped to 1.4 and I feel terrific. Two months ago, I was having in difficulty walking upstairs and attending the NICE meeting on January 5th would have been very difficult. Now, I'm fit and well and looking forward to resuming my two hobbies, dingy sailing and hill walking. Something I haven't been able to do for over two years. Nothing short of miraculous! It must be stressed that Abiraterone is not just about giving someone a few more precious months of life with their loved ones, but it's affect can be long lasting and truly life changing. It has the potential to give a man back his life and keep him in full employment, looking after his family, instead of claiming benefits to keep them. That is a huge and important improvement in quality of life, especially when we are going to have to work until we are 70 years old in the not too distant future. Abiraterone is very easily administered, just four tablets per day and very well tolerated. In the vast number of cases, the side affects are no worse than those of hormone treatment, which is something anyone who needs this drug, will be well used to. Indeed, by now, I don't even consider these to be side affects at all. It has to be said that 10,000+ men die every year of prostate cancer and NICE having just refused Cabaxitaxel, this is the only EoL treatment being considered. In the light of your judgment, one has to wonder whether it is your intention to hope that we are all going to die with as little fuss as possible. Just to underline the importance and success of Abiraterone, the gentleman who was supposed to be the Prostate Cancer Support Federation representative to the NICE committee, Mike Lockett, was refused this drug and	Comments noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).

Consultee	Comment	Response
	died before the consultation could take place. I stepped into his shoes and fortunately for me, I was given Abiraterone and look forward to many more years of quality life.	
Prostate Cancer Charity	**Abiraterone and the end of life drug criteria** The Prostate Cancer Charity believes a significant factor for abiraterone not to be recommended in the draft decision was the committee's conclusion that the patient population size for which abiraterone is indicated is too large for it to be considered as an end of life drug. We are unclear what robust evidence this decision was based on. According to the information provided in the ACD by the drug manufacturer, the size of the population that is likely to be eligible for abiraterone is 3,300. We understand that this is only an estimate as exact numbers of patients at different stages of prostate cancer do not exist. This estimate falls well below the figure of 7,000 outlined by NICE as the normal maximum patient population size for consideration within the end of life drug criteria. The Charity would therefore like NICE to explain why it considers the patient population size indicated for abiraterone to be too large for it to be considered within the end of life criteria. Specifically, we would like further clarity about the source of the evidence offered by a commissioning expert during the STA committee meeting (see 4.19 of the ACD, page 34) that the manufacturer estimates of number of people eligible were underestimates of the number of patients who would receive abiraterone in clinical practice". The evidence that underpins the statement made by this expert has not been referenced and it is not clear, therefore, how robust it is. The Charity notes that sunitinib, which is used to treat advanced kidney cancer, was approved by NICE in 2009 as an end of life drug and appears to be indicated for similar a size of patient population as abiraterone. It is also provides a similar average extension to life. We believe that the sunitinib FAD highlights significant inconsistencies in the recommendations of different NICE committees for different drugs, under the end of life criteria. We would like the committee to clarify why sunitinib was considered to be an end of life drug and abiraterone in this indication has not been, even though the size of the patient populations are comparable.	**End of Life Criteria** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).

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	Furthermore, we have noted that the All Wales Medicines Strategy Group (AWMSG) recently reviewed abiraterone and did consider it to be an end of life drug. We therefore cannot understand why the NICE committee have not reached the same conclusion. We believe that there is no reason why abiraterone should not be considered an end of life drug and that the current decision in the ACD is unclear, inconsistent and the evidence for it is not well defined. **Improving treatment options for advanced prostate cancer** Currently, the only treatment options routinely available from the NHS for men with metastatic castration-resistant prostate cancer who have had chemotherapy are palliative. For a significant number of men, abiraterone offers the chance of more time to spend with family and friends and a better quality of life for a longer period of time at the end of their lives. The Prostate Cancer Charity considers abiraterone to be one of the biggest breakthroughs in prostate cancer treatment in recent years. Abiraterone blocks testosterone synthesis at a stage when no other hormone therapy is effective, it provides an extension of life with few side effects and it can be taken at home. This 'breakthrough' appears to have been recognised by the committee in point 4.20 (page 34) of the ACD, which states that abiraterone "may offer a step change in treatment because it is life-extending rather than simply palliative". It is therefore a bitter blow that the draft decision is for abiraterone not to be recommended. If NICE fail to recommend abiraterone for men in England and Wales, many men will not have fair access to this important drug. The Charity very much welcomes the recent decision by the AWMSG to recommend abiraterone, as part of the approved Wales Patient Scheme, particularly as they considered it to be an end of life treatment. However, we are greatly concerned that after 2013 the Cancer Drugs Fund will cease to exist in England, and it is unclear what provision will be put in place to enable men in England to access abiraterone through the NHS if it not recommended. The NICE final decision will also over-rule the AWMSG decision, which would leave men in Wales at	Comments noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).

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	risk of inequities in accessing abiraterone from the very near future. Despite the significant disadvantage that men with advanced prostate cancer face, this preliminary decision not to recommend abiraterone, coupled with the previous decision not to recommend *cabazitaxel*, send a clear signal to men that improving the treatment of men with advanced prostate cancer is not a priority. **Abiraterone: what 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. As we stated in our response to the consultation in September 2011, the Charity conducted a paper and online survey of people affected by prostate cancer to find out their opinions on abiraterone for the treatment of metastatic, castration-resistant prostate cancer. 101 people replied to the survey. Of these respondents, 7 were men with prostate cancer who were currently being treated with abiraterone. (Please note that the survey was conducted just before abiraterone was licensed for use in the UK). Of the respondents, about 9 out of 10 said that it is 'very important' for abiraterone to become available to all patients for whom it is clinically appropriate. Many respondents believed that increased survival and a better quality of life were of great importance when very limited treatment options are available. Since the ACD was published on NICE's website, we have been asking people affected by prostate cancer to provide some of their views on the draft decision. Comments have included: *"My cousin has suffered from prostate cancer for some while now, and the availability of abiraterone treatment has provided him with marked improvement, both in terms of medical results and of quality of life."* *"Whilst I recognise that economic constraints influence much - if not all - of life*	Comments noted.

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	at present, I think it entirely regrettable that NICE should make such pronouncements with apparent lack of regard for those who currently benefit from such treatment. The mark of a civilized society must be that it cares for all its members, and particularly for those in the greatest need. This decision, though only draft at present, certainly seems to be based upon financial considerations only, with no regard to those whose lives are directly - and indirectly - affected." *"My husband is 59, still running his own company, ten and a half years after diagnosis. Not exactly fighting fit, our life is restricted, however the only 'benefit' he has ever claimed is his blue badge, because of difficulties in walking, this is only used when he is struggling. If he was not given [abiraterone], we would both be on benefit, I would expect within [a] few months. It is highly likely the company would close, putting 8 people out of work. The drug is overpriced, however in his case the cost is easily covered by the saving."* *"During January 2012 I commenced treatment with abiraterone having been prescribed the drug by my oncologist. I have been able to access this treatment through the Cancer Drug Fund. Firstly I wish to formally put on record my own experience with the drug which even at this early stage has been very little short of remarkable. I am experiencing dramatically less pain and enjoying substantially greater mobility than had been normal for many months prior to the commencement of the treatment. In my case the drug is proving highly effective and these quality of life benefits are both profound and tangible."* The comments above clearly express the benefit abiraterone has given to those individuals at this particular stage of prostate cancer. **Cost of abiraterone** The Charity notes that the Committee was unable to provide a QALY for abiraterone, but the Committee did believe the manufacturer's calculation of £63,200 per QALY was too low. In addition to the points we have made above, we would like to urge the manufacturer to further reduce its cost price of abiraterone for the NHS - if this will allow men with prostate cancer to be able to access this vital drug.	Comments noted. In response to the appraisal consultation document, the manufacturer revised the confidential discount under the patient access scheme agreed with the Department of Health. The manufacturer also amended the economic model to reflect the changes to costs suggested by the ERG. These included changes to administration costs to reflect the costs of oncology

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	Conclusion The Prostate Cancer Charity believes that NICE's preliminary recommendation on abiraterone is unacceptable, given the evidence about the clinical effectiveness of this medicine, which has been acknowledged by the Appraisal Committee. Furthermore, the decision not to include abiraterone in the end of life criteria is unclear, inconsistent and not apparently based on good evidence. We strongly recommend that NICE reconsiders its draft decision, and does not run the risk of causing an inequity in access to this breakthrough drug for men with advanced prostate cancer in England and Wales. However, we also recognise that the cost of the drug could be further reduced for the NHS and urge the drug manufacturer to take this course of action. Between 25th August and 22nd September 2011, The Prostate Cancer Charity surveyed people affected by prostate cancer living in England and Wales for their views on abiraterone. 100 people responded to an online and paper survey. 92% of respondents had been diagnosed with prostate cancer (the others were relatives or friends of someone diagnosed with the disease) and 25% of respondents had advanced prostate cancer. 7 people said they were currently being treated with abiraterone.	outpatient visits and of administering mitoxantrone, and changes to the proportion of patients receiving bisphosphonates following disease progression. As a result of these changes and the revised discount under the patient access scheme, the manufacturer's deterministic base-case ICER for abiraterone compared with prednisolone decreased to £46,800 per QALY gained for the one prior chemotherapy subgroup and to £52,851 per QALY gained for the whole population (see FAD section 3.32).
Royal College of Physicians	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** There is agreement that Abiraterone is an effective, safe and well tolerated drug that prolongs life and improves quality of life. We note the difference of opinion between the company and the ERG on the precise details of cost effectiveness modelling and assignation of health Utility Values, but this is beyond the scope of our professional expertise. We have concerns that the ERG assumes that men who may be offered treatment with Abiraterone have a low Utility Value. Our experts would like to point out that these men generally have few co-morbidities otherwise they would not have been fit enough for the previous docetaxel. Any reduced functionality is generally due solely to their cancer. As a group, in our judgement, they are fitter than average for their years. Abiraterone clearly leads to an improvement in quality of life and pain scores in men with symptoms and delays onset of pain in asymptomatic men. The steep fall off in the trial was a real event and our experts believe that it may represent the ability of the trialists to keep to the protocol and maintain	The Committee noted that the mapping algorithm resulted in pre-progression utility values which were similar to or higher than utility values observed in the age-matched general population. In the Committee's view this might not be reasonable because people with metastatic prostate cancer would be expected to have a poorer quality of life than people without prostate cancer. However, it heard from the manufacturer and consultees that, because patients in the COU-AA-301 trial had few comorbidities and had been fit enough to receive chemotherapy, it was not implausible that they would have a similar health-related quality of life to people of the same age in the general UK population. The Committee also noted that the utility values for the pre-progression state were slightly higher than those used in the ongoing technology appraisal of cabazitaxel for metastatic hormone-refractory prostate cancer (derived from interim analysis of a small

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	patients on drug/placebo even though they were progressing clinically and biochemically. At 3 months radiological confirmation of disease progression would have resulted in a large number of patients coming off drug (placebo) at the same time point. We believe that this means patients are modelled to stay in the pre-progression state for longer in the prednisolone arm than happened in the trial and thus underestimated the real benefit of Abiraterone. We believe that Abiraterone is an innovative drug as it is the first in class of a biologically targeted agent aimed at inhibiting a key pathway in androgen biosynthesis. Studies with this agent have shown that prostate cancers, far from becoming 'hormone-resistant', remain androgen –driven and indeed are androgen super-sensitive, in that they synthesise and respond to low levels of their own androgen. Abiraterone is the drug that has led to a redefinition of the disease states in prostate cancer (although our experts are consistently reminded that patients do not like the term 'castrate-resistant'). Another economic consequence of this appraisal would be that UK participation in future international cancer trials is significantly reduced, as NHS standard practice is significantly different from the rest of the international community. The patient representatives on the NCRI Prostate CSG feel particularly strongly about this, as an important issue additional to the concerns about the availability of the drug to suitable patients. For patients whose treatment would have otherwise been funded in a trials setting, the full costs will now fall on the NHS. This deserves to be modelled. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. Our experts believe that there is a serious flaw in the reasoning within the ACD. The Committee accepted that Abiraterone met the criteria of an end-of-life medicine, but felt it did not qualify on the basis that it would be given to a lot of patients (para 4.19). This rule clearly discriminates against people suffering from common cancers (eg breast, prostate and lung cancer) and is unfair. We do not accept the conclusion of the Committee that Abiraterone was <u>not</u> 'licensed for a small population', as, under the definitions provided by	study). The Committee acknowledged a sensitivity analysis from the manufacturer which showed that when a published utility value of 0.715 (from the UK subgroup of Sullivan et al. 2007) was assigned to the pre-progression state, the ICER increased to £51,110 per QALY gained for abiraterone compared with prednisolone. However, the Committee was aware that the utility value taken from Sullivan et al. was based on a small patient subgroup and that this study may have included patients at different stages of prostate cancer. Additionally, the Committee also heard from one clinical specialist that the estimated utility gain for abiraterone compared with prednisolone may have been underestimated and, as a result, the ICER may have been overestimated. The Committee concluded that there was uncertainty about the validity of the utility values for the pre-progression health state derived from the manufacturer's FACT-P mapping algorithm, but that no other robust utility value for the pre-progression health state was currently available (FAD section 4.14). The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line

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	NICE for end-of-life medications, a population is defined as small if it does not normally exceed 7000. In the ACD, NICE has failed to make any estimates of the numbers of patients who might be treated and exactly how big this population would eventually be. It has accepted, without question, Sanofi's estimates of this number at around 3300. Even if this figure were to rise by 20%, as is forecast (by the manufacturer), it would still be well below the 7000 threshold. If the figure of 3,300 is open to dispute, we suggest that NICE should do its own calculations. If the figure of 3,300 is accepted, then we conclude that the Committee has failed to follow its own guidance on this issue. Previous agreed end of life diseases have included a patient population of over 5000, and our view is that the total population of patients with prostate cancer who are fit enough to receive docetaxel falls well short of the approximately 10-12,000 who die of prostate cancer per year in the UK – in some regions it may be as few as 20% of that figure. We accept that there may remain some doubt about the ICER. However, we believe that NICE and Janssen should consider innovative approaches to ensuring patient access to Abiraterone while the uncertainties re ICER are addressed. It is disappointing that the Committee did not include an oncologist. As a consequence, it is not clear that the potential 'cost-benefits' of this novel treatment with a very favourable side-effect profile (as Abiraterone is not a chemotherapeutic agent in the traditional sense) have been appropriately acknowledged and considered. We feel that Abiraterone not only improves survival, but also very effectively controls symptoms and reduces skeletal related events. We believe it will reduce the resources required to look after these patients because of better symptom control.	abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21). The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1). Comment noted. The Committee comprises a group of individuals with a broad range of expertise. Clinical specialists with experience in the management of prostate cancer attended the first Committee meeting to advise the Committee on any clinical issues relating to the disease and to the appropriate use of abiraterone.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support	We are in agreement with the recommendations in the ACD to not to recommend abiraterone for this indication as on the basis of the evidence considered it is unlikely	Comments noted. The final draft guidance recommends the use of

Commentator	Comment	Response
Appraisals Service	that this treatment can be considered cost effective in real life clinical practice. • **The appraisal committee has provisionally concluded that abiraterone is not a cost effective use of NHS resources.** • **The manufacturer's estimate may underestimate the true cost of abiraterone.** The appraisal committee concluded that the manufacturers ICER estimate of £63,200 per QALY was likely to underestimate the true cost because the economic model used to produce it included inappropriate values. The ICER figure of £63,200 includes an agreed patient access scheme involving a single confidential discount to the list price of abiraterone. • **The appraisal committee concluded abiraterone was not licensed for a small population, and therefore, did not meet the full criteria for an end of life treatment.** The manufacturer estimated the eligible population to be 3,690 in 2012 increasing to 4,214 in 2016 for the indication currently under consideration but the committee heard this may be an underestimate. The committee also concluded that even if abiraterone did fulfill the end of life criteria the ICER per QALY would probably still be too high to justify use of limited NHS resources. Abiraterone is currently being considered by a separate NICE STA for the treatment of mCRPC in patients who have not previously received chemotherapy. This additional population should be considered when assessing the total number of people eligible to receive abiraterone in relation to this end of life criteria. Abiraterone is currently licensed for this indication so the Cancer Drugs Fund represents an additional funding source for the potential provision of this drug.	abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1). In the Committee's view, a reasonable starting point for its decision was the manufacturer's base-case ICER for abiraterone plus prednsiolone compared with prednisolone alone of £46,800 per QALY gained for the one prior chemotherapy subgroup (when the discount agreed in the patient access scheme was included). The Committee agreed that the ICER would increase by a small amount if the model correctly accounted for the half-cycle correction to drug costs. The Committee noted that use of a lower utility value for the pre-progression health state or the assumption of a smaller difference in utility between the pre-progression and post-progression health states would further increase the ICER. However, the Committee agreed that more reliable utility values for the pre-progression and post-progression health states were not available. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival. However, the Committee agreed that it was acceptable to use the observed Kaplan–Meier data given the completeness of the survival data in the COU-AA-301 trial.
	• **Using data supplied by the manufacturer, between six and seven (6.59) per 100,000 people are eligible for treatment with abiraterone annually for this indication at a cost of about £164,911.** These figures include the drug cost of abiraterone at £2,930/month (list price) with treatment lasting an average of 8 months and a one off monitoring cost of £1,587.72 per patient. The annual cost	The Committee therefore agreed that once these factors had been taken into account, the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be under

Commentator	Comment	Response
	per patient for the drug and monitoring is £25,028. In 2013-16 the manufacturer predicts a small rise in the number of eligible patients to between 7 and 8 (7.32) per 100,000 people annually, giving a higher cost of approximately £183,200. These figures do not include the patient access scheme discount (redacted in the evaluation report) or the net budget impact of introducing abiraterone on existing treatments (estimated in the manufacturer's submission). • **Evidence for clinical effectiveness is based on a single high-quality phase III RCT (COU-AA-301).** The primary outcome of this study was overall survival, the committee concluded this trial provided persuasive evidence that abiraterone offers a survival advantage to patients. • **Abiraterone is clinically effective at extending overall survival, and survival free of disease progression, compared to a placebo.** Median overall survival was 15.8 months on abiraterone compared with 11.2 months on placebo; absolute difference 4.6 months; HR 0.74, 95%CI 0.64 to 0.86; median follow-up 20.2 months. Time to treatment discontinuation, a proxy measure of survival free of disease progression, was 8 months in those taking abiraterone compared with 4 months on placebo, an absolute difference of 4 months. • **No robust evidence was available to compare the clinical effectiveness of abiraterone with its main clinical comparators mitoxantrone (rarely used in UK clinical practice) or best supportive care.** • **The technology is considered safe and potential adverse reactions are generally manageable and reversible.** These include hypertension, hypokalaemia and fluid retention. • **Abiraterone may offer a step change in treatment for patients because it is life-extending rather than simply palliative.** • **The committee concluded the appraisal should refer to people rather than men because people, who have proposed, started or completed male to female gender reassignment can develop prostate cancer.** This is especially important to note as the cost per 100,000 figures above refer to people and not just men.	£50,000 per QALY gained (FAD section 4.17). **<u>End of Life Criteria</u>** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).
Department of Health	In arriving at its draft recommendations, the Appraisal Committee concluded that the appraisal does not meet the eligibility criteria for the application of the flexibilities for potentially life extending drugs for patients at the end of their lives. I understand that this decision was arrived at on the basis that abiraterone is not licensed for a sufficiently small patient population. Whilst acknowledging that the applicability of the	Comments noted. The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who

Commentator	Comment	Response
	"end of life" criteria was far from the only factor influencing NICE's draft recommendation, it is clearly an important one and we would be grateful if the Appraisal Committee could carefully consider whether or not abiraterone meets the eligibility criteria NICE has set out. In assessing the likely demand for abiraterone, the Committee may find it useful to know the level of clinical demand for abiraterone through the Cancer Drugs Fund. Between April 2011 and the end of January 2012, 904 patients received abiraterone through the Cancer Drugs Fund.	would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).
National Collaborating Centre for Cancer	I believe that not recommending Abiraterone may be considered unfair when compared to the use of Herceptin in patients with breast cancer and NICE may find themselves with a backlash on their hands. I worry that rejecting Abiraterone may impede the development of the drug as something we could use BEFORE chemotherapy (STAMPEDE is looking at this). Why is the cost so high? Could pressure be brought to reduce the cost? Firstly I acknowledge that, although Abiraterone is a very effective drug, with relatively minimal toxicity, its benefit, in terms of prolonged survival at least, is insufficient to justify NICE approval using current cost–effectiveness criteria, even when applying the less stringent criteria for end-of –life cancer treatments. This could be rectified at a stroke if the drug was made cheaper, and it could be argued that all manufacturers of new cancer drugs need to take a long and hard look at their pricing policies, as it could be argued that the more relaxed cost criteria that NICE accepts	Comments noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1). **<u>End of Life Criteria</u>** The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that

Commentator	Comment	Response
	for these drugs allows them to charge higher prices and yet still fit within cost-effectiveness criteria. Having said that, I think the recommendations can be criticised on the basis of the conclusions drawn in para 4.19, which state: 'The Committee agreed that the criteria related to short life expectancy (less than 24 months) without treatment and extension to life (at least 3 months) with treatment were met. However, the Committee concluded that ***abiraterone was not licensed for a small population***, and therefore considered that it does not meet the criteria for an end-of-life treatment.' I am unable to find a definition of 'small population' and it seems unreasonable that a drug of comparative cost-effectiveness are approved simply because they are for patients with rarer cancers It is also disappointing that the appraisal committee did not include an oncologist, and consequently, it is not clear that the potential 'cost-benefits' of this novel treatment with a very favourable side-effect profile (as Abiraterone is not a chemotherapeutic agent in the traditional sense) have been appropriately acknowledged and considered. Accordingly, it is worthwhile noting a comment in the submission from NCRI/RCP/RCR/ACP/JCCO: 'Abiraterone not only improves survival, but also very effectively controls symptoms and reduces skeletal related events. We believe it will reduce the resources required to look after these patients because of better symptom control'. The health economic modelling is very messy. The randomised trial measured quality of life using a different instrument to that required by NICE. It also stopped measuring quality of life on treatment discontinuation so a uniform health utility value (derived from a Swedish study) was applied after that. It might be the case that the abiraterone patients had a different clinical course from the control arm after treatment discontinuation but we will never know this. The conversion of the trial quality of life measurements to the EQ-5D measure required by NICE adds more uncertainty. Basically the manufacturer failed to measure quality of life or health utility values adequately so the health economic modelling is full of uncertainties. NICE has no choice but to make it assessment based on the poor quality cost effectiveness evidence provided (even though the clinical effectiveness is beyond doubt). In the absence of robust cost effectiveness data the only conclusion one can draw from this is that abiraterone is too expensive.	some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21). Comments noted.

Commentator	Comment	Response
NHS Bradford & Airedale	**Clinical effectiveness evidence** Evidence for clinical effectiveness is based on a single high-quality phase III RCT (COU-AA-301). The primary outcome of this study was overall survival, the committee concluded this trial provided evidence that abiraterone offers a survival advantage to patients, compared to placebo. However, it is a single trial. As has been seen in many other new medicines there seems to remain significant uncertainties about how the trial effectiveness plays out in real life. **a) We concur with the advice given to the committee by clinical specialists that participants in COU-AA-301 were likely to be healthier than those who would receive abiraterone in the UK clinical practice, therefore would raise questions about the generalisability of the study to the UK.** The manufacturer carried out a sub-group analysis on patients who had received only one prior chemotherapy regimen; the committee deemed this inappropriate as there was no evidence suggesting a difference in the clinical effectiveness of abiraterone in this subgroup. b) We note the main finding of the net OS advantage (**compared to placebo** – hardly a high bar) of 4.6 months. However we note that the appraisal committee found no **robust evidence was available to compare the clinical effectiveness of abiraterone with its main clinical comparators or best supportive care. We concur that the main active comparator** mitoxantrone is rarely used in UK but that best supportive care is absolutely an appropriate comparator. This is of additional note when you consider that there is published research comparing active treatment and palliative care (lung cancer, NEJM 2010, reference available if required) highlighting that patients receiving early and high quality palliative care experienced less depression, improved quality of life and survived 2.7 months longer than standard care. Though obviously there are differences in biological mechanisms it clearly established that palliative care (which might conceivably be considered Best Supportive Care, and <u>which funding may be reduced for</u> should commissioners be required to fund this treatment) can and does have a clinically important impact. Therefore we believe it is an absolutely relevant comparator when considering the comparative clinical (and cost) effectiveness. c) Given the seeming issues re lack of external validity to the UK population and the lack of comparison to an active comparator, both noted above, this finding of Overall Survival advantage of 4.6 months does not seem particularly credible in the UK population.	Comments noted. The Committee heard from clinical specialists that participants in the COU-AA-301 trial were likely to be healthier than those who would receive abiraterone treatment in UK clinical practice. However, it acknowledged that, in response to the appraisal consultation document, a number of comments from clinical organisations suggested that participants in the COU-AA-301 trial would be similar to patients who would be considered for abiraterone treatment in UK clinical practice (FAD section 4.4). The Committee considered by how much abiraterone extended life. It noted that in the manufacturer's base-case economic analysis the estimated mean overall survival gain for abiraterone was greater than 3 months (median overall survival gain 4.6 months; mean overall survival gain commercial in confidence). The Committee concluded that an improvement of more than 3 months in mean overall survival had been robustly demonstrated (FAD section 4.21).

Commentator	Comment	Response
NHS Bradford & Airedale	**2 Cost effectiveness** a) We concur with the Appraisal Committees view that the manufacturers estimation of £63,200 per QALY is likely to be an underestimate of the true value for money- it would seem obvious that a manufacturer would populate a model with more optimistic assumptions. In addition, given the points raised in point 1c (above) it might be considered inappropriate to simply plug an OS advantage of 4.6 months into an economic model. This, in our view, further and significantly weakens the credibility of the manufacturers presentation of the ICER. b) The ICER figure of £63,200 includes an agreed patient access scheme involving a single confidential discount to the list price of abiraterone. Whether the NHS commissioner (whom ultimately is financially responsible for the investment) actually realizes that discount in cash seems debatable, there are many examples of patient access schemes that, whilst seeming like a good idea within the Department of Health, do not seem to actually work in practice. We can provide examples if the committee would wish. c) In addition, commissioners and providers need to invest (sometimes substantially) in admin resources to make such schemes work – obviously this expenditure may have the net effect of cancelling out any savings that might be seen from the confidential reduction in list price (if indeed it is realized). We would expect that the requirement for additional expenditure on administration to make the PAS work would be reflected or at least taken into account in economic modeling. **3 End of life Criteria** a) We agree that this medicine is not licensed for a small population – estimates of ,690 in 2012 increasing to 4,214 in 2016 for the indication currently under consideration but the committee heard this may be an underestimate. **Thus it seems exceptionally hard to make a case that this indication would meet the end of life criterion.** Even if the EoL criterion did apply, the ICER would still likely be too high to qualify. **4 Potentially eligible population / impact on commissioners / opportunity cost** **a) We would strongly encourage the Appraisal Committee to consider the population impact in epidemiological terms.** **b) Particularly we would wish to draw attention to the impact on other**	In the Committee's view, a reasonable starting point for its decision was the manufacturer's base-case ICER for abiraterone plus prednsiolone compared with prednisolone alone of £46,800 per QALY gained for the one prior chemotherapy subgroup (when the discount agreed in the patient access scheme was included). The Committee agreed that the ICER would increase by a small amount if the model correctly accounted for the half-cycle correction to drug costs. The Committee noted that use of a lower utility value for the pre-progression health state or the assumption of a smaller difference in utility between the pre-progression and post-progression health states would further increase the ICER. However, the Committee agreed that more reliable utility values for the pre-progression and post-progression health states were not available. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival. However, the Committee agreed that it was acceptable to use the observed Kaplan–Meier data given the completeness of the survival data in the COU-AA-301 trial. The Committee therefore agreed that once these factors had been taken into account, the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be under £50,000 per QALY gained (FAD section 4.17). Comment noted. The Committee was asked by the Department of Health to consider the results of the manufacturer's submission with the patient access scheme included. Consideration of the resource implications to PCTs of the patient access scheme is outside NICE's remit. The Department of Health and the manufacturer have agreed that abiraterone

Commentator	Comment	Response
	patients affected by the opportunity cost of a requirement to fund this medicine were the Appraisal Committee to change their initial view c) Manufacturer data (again we would view these to be optimistic under estimates) between six and seven (6.59) per 100,000 people are eligible for treatment with abiraterone annually for this indication at a cost of about £164,911. These figures include the drug cost of abiraterone at £2,930/month (list price) with treatment lasting an average of 8 months and a one off monitoring cost of £1,587.72 per patient. The annual cost per patient for the drug and monitoring is £25,028. d) In 2013-16 the manufacturer predicts a small rise in the number of eligible patients to between 7 and 8 (7.32) per 100,000 people annually, giving a higher cost of approximately £183,200 per 100,000. This would represent a budget impact of c£1m in Bradford and Airedale. We agree with the committee's conclusion that the appraisal should refer to people rather than men because people, who have proposed, started or completed male to female gender reassignment can develop prostate cancer. This is especially important to note as the cost per 100,000 figures above refer to people and not just men. (We accept that these figures do not include the patient access scheme discount (redacted in the evaluation report) or the net budget impact of introducing abiraterone on existing treatments (estimated in the manufacturer's submission). **e)** In epidemiological terms, taking into account response rates, OS advantage and those that do gain benefit AND those that don't, this investment would allow 17 men to have a chance of extending life by two to four months above current or no treatment respectively. f) NHSBA currently (10/11 Programme Budget Data) spends £51m on cancer. Thus a spend of c£1m on medicine equates to almost 2% of the cancer budget spend on one medicine that effectively buys an upper estimate of four months additional survival in those 17 men. This additional expenditure would come at a time when there is absolutely no growth in the NHS, and expectation a net effect (accounting for population growth and demographic change) of £50m being taken out of the baseline budget over the next few years.	will be offered to the NHS under a patient access scheme which makes abiraterone available with a discount on the list price. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the manufacturer (FAD section 5.3). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published (FAD section 2.3). The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when

Commentator	Comment	Response
	h) For this level of expenditure, it seems reasonable to expect this medicine to have a significant effect on survival, life expectancy and possibly mortality rate for prostate cancer. Particularly given the inherent opportunity cost of other treatments forgone. i) We understand and respect the fact that NICE is precluded from considering absolute affordability of its recommendations. However, NHS commissioners (and providers) MUST be mindful of this, indeed it is an absolute duty on PCTs who do not operate in a QALY based method of assessing value - the method is more one based on absolute cost and absolute value in a whole population. Thus opportunity cost is an all consuming factor. j) The opportunity cost would fall on other, anonymous, patients if commissioners were required to make funding available to the relatively small no of patients who would get marginal benefit from this treatment. k) Therefore, when deliberating this further. We would encourage the committee to be mindful of the services that would be reduced in order to make this treatment available. This would inevitably be in treatments that are more cost effective and highly valued by patients than this particular treatment. Inevitably it would seem that this would represent a net social loss of health, and we would encourage the committee to question whether this would be socially acceptable. **In summary** a) We would view this treatment to be of exceptionally High marginal cost for marginal clinical benefit for a tiny proportion of patients. With great opportunity cost, This seems exceptionally poor value to the taxpayer. b) We note that this indication has recently been recommended by AWMSG and that the Welsh don't have the Cancer Drugs Fund as a let out valve for poor value medicines. Whilst we recognise that the CDF is top sliced from NHS Commissioners baseline budgets, those NHS Commissioners have little to no control over this. We would be of the view that this medicine ONLY has a place as a candidate (alongside many other medicines of poor cost effectiveness) for consideration within the CDF. However we would even question its place there. That would clearly be a decision beyond the remit of a NICE TA. **Certainly our view is that this medicine should have no place in being funded as part of NHS pathway that NHS commissioners have influence over**	estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21). Comments noted. It should be noted that, as part of the appraisal process, the Committee is instructed (in accordance with the NICE Methods Guide) to consider the opportunity costs associated with the use of the technology being appraised. The additional analyses submitted by the manufacturer in response to the ACD are included in the evaluation report for this appraisal. These analyses were discussed by the Committee, along with all comments from other consultees and commentators during the second Committee meeting.

Commentator	Comment	Response
	c) Finally, we are aware of additional information that has been submitted by the manufacturer at a late stage. We have not seen this, and as such are blind to any implications in might have for the views we express here. We would hope to be able to review this additional information.	
NHS Hertfordshire	**The appraisal committee has provisionally concluded that abiraterone is not a cost effective use of NHS resources.** We are in agreement with the recommendations in the ACD to not to recommend abiraterone for this indication. On the basis of the evidence considered, the cost/QALY, and the potential likely numbers of patients, this treatment is unlikely to be cost effective in real life clinical practice, which is less controlled than clinical trials. We are also concerned that some of the data submitted by the manufacturer to the ERG committee, was not available to us for review. **The manufacturer's estimate may underestimate the true cost of abiraterone.** The appraisal committee concluded that the manufacturers ICER estimate of £63,200 per QALY was likely to underestimate the true cost because the economic model used to produce it included inappropriate values. The ICER figure of £63,200 includes an agreed patient access scheme involving a single confidential discount to the list price of abiraterone. NHS Hertfordshire does have concerns about the value-for-money of an ICER of £63,200 and if this is underestimated because the model did not include appropriate values, this would make this treatment even less cost-effective. **The appraisal committee concluded abiraterone was not licensed for a small population, and therefore, did not meet the full criteria for an end of life treatment.** The manufacturer estimated the eligible population to be 3,690 in 2012 increasing to 4,214 in 2016 for the indication currently under consideration but the committee heard this may be an underestimate. The committee also concluded that even if abiraterone did fulfill the end of life criteria the ICER per QALY would probably still be too high to justify use of limited NHS resources. Feedback received from clinicians advising NHS Hertfordshire indicates that whilst initially the number of patients qualifying for treatment may be about 40 in a million population per year (based on current uptake of docetaxel), eventually many more patients in this stage of the disease will be willing to try docetaxel with the hope of accessing abiraterone. NHS Hertfordshire agrees that the ICER per QALY and the potentially higher numbers of patients likely to go on this treatment would not justify the use of limited NHS resources. NHS Hertfordshire estimates that about £1m would need to be invested for this treatment to treat about 40 patients for an overall survival benefit of 4 months. This would be a lower priority	Comments noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1). In the Committee's view, a reasonable starting point for its decision was the manufacturer's base-case ICER for abiraterone plus prednsiolone compared with prednisolone alone of £46,800 per QALY gained for the one prior chemotherapy subgroup (when the discount agreed in the patient access scheme was included). The Committee agreed that the ICER would increase by a small amount if the model correctly accounted for the half-cycle correction to drug costs. The Committee noted that use of a lower utility value for the pre-progression health state or the assumption of a smaller difference in utility between the pre-progression and post-progression health states would further increase the ICER. However, the Committee agreed that more reliable utility values for the pre-progression and post-progression health states were not available. The Committee also noted that the ICER would increase slightly if a parametric curve were used to model overall and progression-free survival. However, the Committee agreed that it was acceptable to use the observed Kaplan–Meier data given the completeness of the survival

Commentator	Comment	Response
	compared to other services that need development. **Using data supplied by the manufacturer, between six and seven (6.59) per 100,000 people are eligible for treatment with abiraterone annually for this indication at a cost of about £164,911.** These figures include the drug cost of abiraterone at £2,930/month (list price) with treatment lasting an average of 8 months and a one off monitoring cost of £1,587.72 per patient. The annual cost per patient for the drug and monitoring is £25,028. In 2013-16 the manufacturer predicts a small rise in the number of eligible patients to between 7 and 8 (7.32) per 100,000 people annually, giving a higher cost of approximately £183,200. These figures do not include the patient access scheme discount (redacted in the evaluation report) or the net budget impact of introducing abiraterone on existing treatments (estimated in the manufacturer's submission). From the manufacturer's estimate, the numbers likely to need treatment are almost double those estimated by NHS Hertfordshire based on current use of docetaxel. However, as we have stated previously, our local specialists have indicated that any current estimate is much lower than what we are likely to see in the future. Based on this, it is NHS Hertfordshire's view that this technology does not meet the end of life criteria. **Evidence for clinical effectiveness is based on a single high-quality phase III RCT (COU-AA-301).** The primary outcome of this study was overall survival, the committee concluded this trial provided persuasive evidence that abiraterone offers a survival advantage to patients. **Abiraterone is clinically effective at extending overall survival, and survival free of disease progression, compared to a placebo.** Median overall survival was 15.8 months on abiraterone compared with 11.2 months on placebo; absolute difference 4.6 months; HR 0.74, 95%CI 0.64 to 0.86; median follow-up 20.2 months. Time to treatment discontinuation, a proxy measure of survival free of disease progression, was 8 months in those taking abiraterone compared with 4 months on placebo, an absolute difference of 4 months. **No robust evidence was available to compare the clinical effectiveness of abiraterone with its main clinical comparators mitoxantrone (rarely used in UK clinical practice) or best supportive care.**	data in the COU-AA-301 trial. The Committee therefore agreed that once these factors had been taken into account, the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be under £50,000 per QALY gained (FAD section 4.17). The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).

Commentator	Comment	Response
	The technology is considered safe and potential adverse reactions are generally manageable and reversible. These include hypertension, hypokalaemia and fluid retention. **Abiraterone may offer a step change in treatment for patients because it is life extending rather than simply palliative.** **The committee concluded the appraisal should refer to people rather than men because people, who have proposed, started or completed male to female gender reassignment can develop prostate cancer.** This is especially important to note as the cost per 100,000 figures above refer to people and not just men. NHS Hertfordshire would ask the NICE appraisal committee to note the following: • There is no growth in NHS funding for the next 5 years. The inflation in NHS means that the NHS has to reduce its spend by £5bn a year. • Whilst the NICE does not have the remit to consider affordability, commissioners have this responsibility. • Without any growth in NHS resources, the only way commissioners can afford a NICE approved treatment is by disinvesting from other services / treatments. As the cost/QALYs of all such services / treatments are not available, we are not able compare existing treatments/ services with NICE recommended treatments. it is very likely that prioritising a NICE recommended treatment may result in disinvesting from a service / procedure/treatment that is of better value to the NHS. • Whist patient access schemes may appear to make a treatment more cost-effective for the NHS, the management of these schemes has resulted in a lot of work for commissioners and providers. In reality, commissioners (and therefore the NHS) has not always been able to recover the money spent. • We believe that pressure should be put on the manufacturer to provide this product at a much more reasonable price without a patient access scheme. In summary, in the current NHS climate, the NICE end-of-life criteria need reviewing to ensure that the NHS does not lose services that ultimately offer better value overall.	Comments noted.

Summary of comments received from members of the public

Theme	Response
End-of-life Criteria The Committee has overestimated the number of people with castration-resistant prostate cancer who would be eligible for abiraterone after previous docetaxel chemotherapy.	Comment noted. The Committee was aware that the population included in the marketing authorisation was likely to be larger than that for cabazitaxel given that abiraterone can be administered at home, and that some patients who would be unlikely to tolerate chemotherapy might take abiraterone. The Committee understood from estimates obtained from the appraisal of cabazitaxel that approximately 3500 people with hormone-refractory metastatic prostate cancer received docetaxel in England and Wales in 2011, and that, according to estimates provided by the manufacturer, approximately 70% of these (n = 2500) would be able to receive second-line abiraterone treatment in line with the marketing authorisation. The Committee noted from the manufacturer's response to the appraisal consultation document that in the future abiraterone may be licensed for use earlier in the treatment of castration-resistant prostate cancer but acknowledged that any future extensions to the marketing authorisation remain uncertain and should not be taken into consideration when estimating the number of patients currently eligible for treatment. In the Committee's view, abiraterone was licensed for a small population and therefore meets the criteria for an end-of-life treatment. (FAD section 4.21).
Lack of other available treatments for mCRPC There are currently no other treatments widely available on the NHS across the UK for men who have metastatic castration-resistant prostate cancer which has stopped responding to hormone therapy and chemotherapy. The only other options are palliative.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Survival benefit of abiraterone The average survival benefit period of abiraterone treatment is stated as 4 months but we would like this to be reviewed by NICE as we understand in the UK no-one died before the 6 month period and there are some people still living after 6 years.	Comment noted. The Committee discussed the results for the COU-AA-301 trial and noted that abiraterone was associated with a statistically significant improvement in overall survival and progression-free survival compared with prednisolone for both the whole (intention-to-treat) population and the manufacturer's base-case population (one prior chemotherapy subgroup). The Committee also noted that patients receiving abiraterone were more likely to experience an improvement in symptoms, including pain, functional status and fatigue. The Committee therefore concluded that the evidence demonstrated that abiraterone was an effective second-line treatment for castration-resistant metastatic prostate cancer (FAD section 4.6).

Theme	Response
Benefits of oral treatment The importance of these benefits to the patients and in a wider sense, to their families is clear, enabling extension of life, reduction in pain and resumption in many cases of previously enjoyed mobility. Abiraterone has very few side-effects beyond what prostate cancer patients are already used to in their previous treatment. The ability of the patient to take abiraterone therapy by mouth (and therefore potentially at home) has enormous benefits, both financial and psychological,to many patients and would also reduce the burden to the NHS.	Comment noted. The Committee heard from the patient experts that the most important benefits of abiraterone were extension to life and improved quality of life, including less pain and improved mental and physical health. The Committee heard that patient experts believed that adverse reactions to abiraterone treatment were tolerable and comparable to those associated with hormone treatment. The patient experts also commented that another advantage of abiraterone is that patients can take it orally at home (see FAD section 4.3).
Disagreement with provisional guidance It is disappointing that the provisional recommendation is not positive.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Benefits not captured in QALYs Insufficient weight has been given to the improved quality of life and improved palliation on this drug. The benefits to patients' families and the ability to help people remain in employment have also not been captured in the QALY measure.	Comment noted. The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. The Committee considered that abiraterone may offer a step change in treatment because it is life-extending rather than simply palliative but that this element of innovation would already be accounted for when moving from an ICER of £20,000 to £30,000 per QALY gained. The Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home rather than needing a hospital visit, and is associated with few adverse reactions. The benefit related to being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. The Committee therefore acknowledged that abiraterone provides health-related quality of life benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone, and that the ICER would decrease when these benefits were taken into consideration (see FAD section 4.19).
Generalisability of clinical evidence The population included in the pivotal study had previously received docetaxel however, only 45% of them had previously progressed with docetaxel. So, the population included in the indication (progressed to docetaxel) is not the same as the study population (pretreated, including progression, not progression,	Comment noted. The Committee heard from clinical specialists that participants in the COU-AA-301 trial were likely to be healthier than those who would receive abiraterone treatment in UK clinical practice. However, it acknowledged that, in response to the appraisal consultation document, a number of comments from clinical organisations suggested that participants in the COU-AA-301 trial would be similar to patients who would be considered for

Theme	Response
intolerance...). In conclusion, the study population is more favourable than the indication population and the results obtained do not correspond to that in the target population.	abiraterone treatment in UK clinical practice (See FAD section 4.4).
NICE Methods – Decision based on cost Why should cost enter the equation surely if it prolongs a persons life cost is immaterial.	Comment noted. When making its decision, the Committee has considered all of the clinical and economic evidence provided by the manufacturer and the Evidence Review Group as well as the submissions and statements from patient groups, professional organisations, clinical specialists and the general public. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Proposed review date of April 2015 is too late If negative decision remains review date must be sooner.	The guidance will only be reviewed when new evidence becomes available which is likely to impact on the current recommendations.
Appropriateness of 'one prior chemotherapy' population We would disagree with the Committees assumption that it was not appropriate to restrict the population considered in the basic analysis to the sub group failing one prior chemotherapy treatment. Urologists and Oncologists in the United Kingdom would argue that this assumption is correct and accurately reflects the population of castration-resistant prostate cancer patients. Currently patients would rarely receive more than one chemotherapy.	Comment noted. The Committee heard that the manufacturer considered the number of prior chemotherapies sufficiently important as a prognostic factor (in that more than one chemotherapy would imply a later stage of disease, more previous adverse reactions and more treatment-resistant tumours) to include it as a stratification factor for randomisation. The Committee also heard from the manufacturer that the difference in relative median overall survival benefit for abiraterone between the one prior chemotherapy subgroup and the subgroup who received more than one prior chemotherapy was supported by results for progression-free survival and other related outcomes from the COU-AA-301 trial. The difference was also supported by overall survival results from published studies of other second-line treatments for castration-resistant metastatic prostate cancer. The Committee accepted that this population was likely to reflect patients who would be treated with abiraterone in UK practice, and who would have better treatment outcomes because they have less advanced disease. Therefore, the Committee concluded that it was reasonable based on biological plausibility and the pre-specification of this group in the COU-AA-301 trial (as a stratification factor) to accept this patient subgroup and its associated effectiveness data as the base-case for the analysis (FAD

Theme	Response
	section 4.7).
Price of abiraterone set by the manufacturer is too high Generous public donations to Cancer Research UK and other organisations paid for the initial development of the drug and it is disappointing that the drugs manufacturer couldnt offer NICE a price they could agree on. I feel NICE should get round the table with the suppliers to negotiate a better price for NHS patient treatment for the benefit of sufferers.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Equalities Prostate cancer, unlike the equivalent cancer in women i.e. breast, is vastly underrepresented in terms of pharmaceutical interventions, particularly in the case of progressive castration-resistant metastatic prostate cancer.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
NICE Remit Why is NICE's remit not expanded to include the ability to negotiate drug prices and other monetary arrangements?	Comment noted. Patient access schemes are special ways that pharmaceutical companies can propose to enable patients to gain access to high costs drugs. The Patient Access Scheme Liaison Unit (PASLU) has been set up by NICE to work with manufacturers who are considering a patient access scheme for their drug or treatment. The Patient Access Scheme Liaison Unit (PASLU) looks at the proposal made by the manufacturer to see if it is a scheme that would work in the NHS. The manufacturer of abiraterone has agreed a patient access scheme with the Department of Health. This involves a single confidential discount applied to the list price of abiraterone. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published (FAD section 2.3).
Transparency Why is this discount under the patient access scheme confidential? Patients need to make informed choices about treatment. This is not easy if pricing information is not easily accessible.	Comment noted. NICE considers it essential that patient access schemes can be received and considered in confidence. NICE also understands that manufacturers may experience commercial and other harm if information on the detail of proposed schemes were made publically available at this point. Therefore, NICE will treat all details of proposed schemes as confidential and will not release any information relating to it under the Freedom of Information Act or in any other circumstance, unless the manufacturer has agreed to the release.

Theme	Response
Access to abiraterone (compared to Europe) If not approved by NICE, people will be denied an effective treatment that is available in other countries.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Negative impact on future UK research Non-recommendation of abiraterone for cost reasons would send the wrong signal to drug manufacturers in their research for medical breakthroughs of any nature and in particular cancer, including prostate cancer.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Abiraterone and ongoing research In response to the cost effectiveness concerns over abiraterone, NCRI Prostate CSG members and others have formed a Trial Management Group and submitted a trial application to the HTA. FASTRAC is a trial which exploits the abiraterone food effect. Abiraterone has the most marked food effect of any drug in medicine. Bioavailability is increased five to ten fold if the drug is given with a meal. Yet the manufacturers recommend that four tablets (1000mg) be taken on an empty stomach. In FASTRAC we propose restricting abiraterone to a cost effectiveness trial, in which one tablet taken immediately after a meal is compared to four tablets taken on an empty stomach. This trial would save over £19million in drug costs and would be a less costly route to providing access to abiraterone. One option for the NICE panel would be to liaise with the HTA and recommend abiraterone only within the FASTRAC trial. This would link the research and policy arms of the NHS for the first time and provide a new approach to the provision of costly new cancer drugs. The full HTA FASTRAC protocol is available on request from the Prostate CSG Chair.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).
Impact of negative recommendation – postcode lottery Unless NICE recommends that the costs of abiraterone should be covered by the NHS, men with advanced prostate cancer in England and Wales will face a postcode lottery trying to access this important new medicine. This is unacceptable.	Comment noted. The final draft guidance recommends the use of abiraterone in combination with prednisone or prednisolone as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if their disease has progressed after one docetaxel-containing chemotherapy regimen, and the manufacturer provides abiraterone with the discount agreed in the patient access scheme (FAD section 1.1).