NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer [ID945]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer [ID945]

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4. **Additional expert responses received post appeal committee meeting**
   a. **Dr Noel Clarke, Clinical expert** - nominated by British Association of Urological Surgeons (BAUS)
   b. **Dr Nicholas James, Clinical expert** - nominated by Janssen

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Prostate Cancer UK	The ACD, which recommended against the approval of abiraterone in newly diagnosed high-risk metastatic hormone sensitive prostate cancer, focused mainly on two key issues. Firstly, the document informs us that, at the price offered by the manufacturer to NHS England, abiraterone does not meet NICE's cost effectiveness threshold for recommendation against either docetaxel or androgen deprivation therapy (ADT), the current standard of care. Secondly, the document asserts that the benefit of abiraterone for those unsuitable for docetaxel chemotherapy is unknown. We feel there are flaws in both of these reasons for rejection.	Thank you for your comment. Please see responses to individual comments below.
2	Consultee	Prostate Cancer UK	While Prostate Cancer UK cannot comment specifically on the price, we are concerned that NICE has released this ACD quickly after the latest committee meeting without fulfilling an appeal point upheld by the Appeal Panel. This concerned "the committee's conclusions on cost effectiveness are opaque because it did not provide an ICER range". We recognise that the availability of docetaxel means cost-effectiveness in the whole population is challenging. However, for the group of patients unsuitable for chemotherapy, there is potential to achieve cost-effectives against ADT as abiraterone provides significant comparator clinical benefit. Given the challenges to demonstrate treatment effect in these patients, because the evidence specific to age is underpowered and there is otherwise no evidence available, it is not possible to calculate an ICER specifically for this sub-group. There is, however, a clear unmet need in this sub-group who, without access to either docetaxel or abiraterone, are denied an average additional 15 months of life. They cannot simply be denied this extensive benefit because their age, frailties and comorbidities prevent them from participating in trials with large enough numbers to provide statistically significant evidence. On this basis and to ensure their unmet need is met, the committee should use the proxy of the whole population benefit of abiraterone against ADT as the comparator. This is the means by which an ICER range can be calculated. A final price negotiation can and must then happen before NICE finalises its decision.	Thank you for your comments. The committee noted the unmet need in the population who cannot take docetaxel. It agreed that the clinical effectiveness of abiraterone in this population was uncertain but acknowledged that there were no alternative sources of evidence. It therefore considered the treatment effect from the LATITUDE whole population, but the ICERs remained above the range considered a good use of NHS resources. It was not possible to publish a narrow range of ICERs because the cost effectiveness estimates using list prices have been previously published and the company stated that this would allow back calculation of its discount for abiraterone. See FAD section 3.2, 3.10 and 3.22.

3	Consultee	Prostate Cancer UK	We are concerned that the Committee is requiring specific evidence of treatment effect in the sub-group of patients that are unsuitable for chemotherapy. This evidence is not available. Trial populations often consist of patients that are fitter on average than the general patient population in any given condition.[i,ii] Ordinarily this does not prevent approval for the treatment in the whole population if it is shown to be effective within a trial population, as abiraterone in this indication has been. In this instance, those patients who are unable to have docetaxel are a sub-set of the population who are more likely to not be included in trials due to their older age and potential for poorer performance status. Despite this, the Committee has seen evidence showing that the abiraterone arm of the STAMPEDE trial included some men unsuitable for chemotherapy because there was an increase in the median age of the patient population accessing the abiraterone trial arm after the docetaxel trial arm closed. This patient population also contained increased frailty characteristics because of chemotherapy ineligibility. The evidence also shows that this patient population had favourable overall survival outcomes to the docetaxel trial arm population (HR 0.59 compared to HR 0.69, respectively). Clinical experts have also said that there is no biological reason for any difference in efficacy of abiraterone in chemo-suitable and -unsuitable populations, as the two treatments' modes of action are completely different.	Thank you for your comments. The committee considered using age, performance status and year of recruitment to STAMPEDE to represent people who cannot or should not have docetaxel. However, it agreed that the subgroups did not specifically reflect the population for whom docetaxel is contraindicated or unsuitable. At the fifth appraisal meeting the committee acknowledged that evidence specific to people who cannot or should not take docetaxel was not available, so it considered the treatment effect from the whole population it its decision making. See FAD sections 3.10, 3.11 and 3.21.

4	Consultee	Prostate Cancer UK	The Committee recognises that one determining factor for the patients that are unsuitable for chemotherapy is older age. We have shown that this factor correlates strongly with reduced chemotherapy use in our analysis of Public Health England data. The ACD also makes clear that age alone is not the only factor, and that chemo-unsuitability is based on several factors. Despite recognising that there are numerous factors which determine chemo-unsuitability, the ACD focuses on data specific to age from LATITUDE, from a small sub-group that therefore gives high uncertainty, as a suggestion that abiraterone might be less effectives in a chemo-unsuitable population. The HR for OS for abiraterone + ADT compared to ADT alone is 0.86 (95% CI 0·62 to 1·21) for people 75 years and over. It is not possible to determine the impact of age on the effectiveness of abiraterone from a small population, especially as increasing age is associated with a greater number of co-morbidities and poorer health status - both acting as confounding factors. This should not be used as evidence that abiraterone is less effective in a chemo-unsuitable population. The Committee should instead focus on benefit in the whole trial population, which is proven with a high degree of certainty. Indeed, this has previously been accepted for this drug in the castrate resistant setting. In the COU-AA-302 study, which investigated the impact of abiraterone in chemotherapy-naïve men with metastatic castrate resistant prostate cancer, men with a performance status of 1 showed less efficacy, with a HR of 0·87 (0·65–1·16) compared to 0·79 (0·66–0·93) for men with a performance status of 0. Yet, the committee reviewed the benefit of the overall population as an indication of the treatment, and thus should take the same approach in this instance.	Thank you for your comment. The committee noted that subgroup data should be interpreted with caution as it was based on a small number of people and did not specifically reflect the population for whom docetaxel is contraindicated or unsuitable. It therefore considered the whole population treatment effect in its decision making. See FAD sections 3.10 and 3.11.
5	Consultee	Prostate Cancer UK	Without any other available evidence, the only way to collect data on this chemo-unsuitable sub-group would be through real-world evidence gathering, potentially from the use of abiraterone in Scotland, where it is approved, or from Wales during the COVID pandemic. However, this would place an administrative burden on the NHS. Additionally, the data would not be timely, and the cohort may still not be of sufficient size to reach statistical significance. We would also note that abiraterone was approved for the whole population for use before chemotherapy in men with castrate-resistant disease, and there is a strong likelihood that men unsuitable for chemotherapy will be accessing and benefitting from it. On this basis, there should be no reason to assume that abiraterone could not benefit these patients earlier in the pathway if whole population evidence is used.	Thank you for your comment. At the fifth appraisal meeting, the committee considered alternative sources of data for the subgroup of people who cannot have docetaxel. However, it concluded that there are no available sources that have not been considered as part of this appraisal. See FAD section 3.10.

6	Consultee	Prostate Cancer UK	By requiring more specific evidence and not applying the significant benefit of abiraterone over the standard of care (ADT) in the whole population, the Committee is setting a precedent. Other treatments in the appraisal pipeline for this indication will be unlikely to have this evidence either. They will also likely struggle to achieve cost-effectiveness in comparison to docetaxel. This has the potential to block patients unsuitable for chemotherapy from having any treatment other than ADT and will see them continue to lose out on additional months of life just because they cannot tolerate chemotherapy, despite effective alternatives existing.	Thank you for your comment. The committee considered ICERs using the treatment effect from the LATITUDE whole population to represent people who cannot or should not take docetaxel. However, cost effectiveness estimates remained above the range considered a good use of NHS resources See FAD section 3.21

7	Consultee	Prostate Cancer UK	STAMPEDE is the main trial with evidence of abiraterone's effectiveness in men with metastatic hormone-sensitive prostate cancer (mHSPC). Evidence drawn from two arms of this trial showed that, in 2013, the docetaxel arm of the trial closed but the trial continued to recruit to the ADT alone and abiraterone in combination arms (among others). This meant people recruited to the trial from this point could have included people for whom docetaxel was contraindicated or unsuitable, because there was an increase in the median age of the patient population accessing the abiraterone trial arm after the docetaxel trial arm closed. This patient population also contained increased frailty characteristics because of chemotherapy ineligibility. However, the Expert Reference Group (ERG) highlighted, and the Committee agreed, that this did not provide the evidence specifically for the group of patients in whom docetaxel was contraindicated or unsuitable. This was because the 2013 to 2014 data would also have included people who could have docetaxel". The ACD states regarding this point that "data specific to this group was not presented to the committee. The committee concluded that assessing data specific to the relevant population was preferred." As a trial specific to this population cannot be carried out, we are left with the data from the existing key trials: LATITUDE and STAMPEDE. We have discussed with the lead statistician from STAMPEDE the possibility of extracting only those participants unsuitable for docetaxel, using the criteria included in the ACD. Unfortunately, limitations in the data mean that it is not possible to do so. This is because the criteria for exclusion from the trial were similar to the criteria contained in the ACD, including patients with baseline neutrophil count of <1,500 cells/mm and patients with a performance status of 3 or 4 (plus only a limited number of patients with performance status 2 in the trial). Further, certain criteria such as those who might be hypersensitive to the active substance in docetaxel were not recorded for participants entering the trial. Without further evidence availability that is specific to the criteria set for the chemotherapy unsuitable population, whole population data should be used to prevent denying these patients access to a life extending treatment, now and in the future.	Thank you for your comments. At the fifth appraisal meeting, the committee agreed that the LATITUDE and STAMPEDE subgroups did not specifically reflect the population for whom docetaxel is contraindicated or unsuitable. It considered the treatment effect from the whole population it its decision making. See FAD sections 3.10, 3.11 and 3.21.

8	Consultee	Prostate Cancer UK	Given the previous points, the ACD therefore fails to recognise that that it is not possible to obtain the evidence of effectiveness of abiraterone "specific to the relevant [chemo-unsuitable] population". It cannot be extracted from any existing trials or generated in a new trial. The consequence is that, despite abiraterone showing good efficacy across the entire trial populations, the subset of these men for whom there is no alternative treatment will progress to hormone refractory disease more quickly. They can only access abiraterone or enzalutamide when their prostate cancer is much harder to live with and their survival benefit greatly reduced. These patients have the potential to benefit from an additional 15 months of life when receiving abiraterone while their disease remains hormone sensitive. However, this benefit decreases to 4 months of additional life when given at the metastatic castrate resistant stage of disease. As well as this shortened life, these men also lose several months with a better quality of life while disease progression is delayed.	Thank you for your comment. The committee was aware of the larger survival benefit compared with ADT alone when abiraterone was used earlier in the treatment pathway. However, it agreed that its remit was to appraise abiraterone in the proposed indication and not to identify the best order and sequence of treatments. See FAD section 3.7.
9	Consultee	Prostate Cancer UK	*Our overall response to the ACD is to call upon the Committee to recognise the lack of their preferred evidence, and the precedent this evidence preference will have for the other treatments in this indication that NICE is appraising including enzalutamide and apalutamide. If this decision is made final, the committee is shutting the door on men in this situation ever having approved access to any treatment for their condition until they are castrate resistant when treatment benefits and quality of life are greatly reduced. We call upon the committee to recognise that the trial evidence in the full population would in any other situation be considered enough to approve the treatment, as explained in our reasoning above. The strength of the evidence of the benefit of abiraterone in the whole trial population from both LATITUDE and STAMPEDE means the committee should approve abiraterone for men with high risk hormone sensitive metastatic prostate cancer who are unsuitable for docetaxel chemotherapy, conditional upon a price agreement with NHS England that produces an acceptable ICER.*	Thank you for your comment. The committee considered ICERs using the treatment effect from the LATITUDE whole population to represent people who cannot or should not take docetaxel. However, cost effectiveness estimates remained above the range considered a good use of NHS resources. See FAD section 3.21

N/A	Company	Janssen	Janssen welcome the opportunity to comment on the appraisal consultation document (ACD) for abiraterone in newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC). Janssen are pleased to see that the Committee have recognised and agreed the need to consider separately the subgroup of patients in whom docetaxel is contraindicated or unsuitable. This is an area of great unmet need where life expectancy is no more than three years. We are, however, exceedingly concerned that the Committee's conclusions, regarding the clinical evidence for abiraterone in these people, and the respective ramifications this has for cost-effectiveness, do not provide sound basis for of the negative recommendation. The Committee's perceived uncertainty in the data supporting use of abiraterone in people who are contraindicated or unsuitable for docetaxel has led to the Committee concluding that there are no appropriate estimates for cost-effectiveness. Janssen are therefore unable to resolve cost-effectiveness concerns and such conclusions have detrimental ramifications for patient access to abiraterone which would fulfil an unmet need in this setting.	Thank you for your comment. Please see responses to individual comments below.

1	Company	Janssen	Janssen are concerned that statements in the ACD, regarding data for abiraterone in people for whom docetaxel is contraindicated or unsuitable, fail to acknowledge the relevance of the evidence that is available. In Section 3.11 in the ACD it states: *"No data were presented specifically for the group of people who cannot take docetaxel."* It is not possible for Janssen to present comparative data solely for abiraterone plus ADT versus ADT alone in the group of people for whom docetaxel is contraindicated or unsuitable, nor do we believe it is reasonable for the committee to insist on this for the purposes of decision-making. As highlighted through the framework proposed in Section 3.3. of the ACD, there are many factors that determine whether a patient is suitable for docetaxel, but these were not collected as part of the LATITUDE or STAMPEDE trials and so it is exceedingly challenging to retrospectively identify a subgroup which mirrors this framework. Nevertheless, unsuitability for docetaxel was not an exclusion criterion in the LATITUDE trial, nor would it have precluded patients from enrolment to the abiraterone arm of STAMPEDE trial, after the closure of the docetaxel arm. It is therefore valid to suggest that people who would otherwise meet the framework outlined in Section 3.3, may already exist in the LATITUDE and STAMPEDE datasets. Results from LATITUDE and STAMPEDE are no less generalisable than most oncology trials and therefore Janssen are concerned that the Committee's assertion will prevent this unmet need from being fulfilled. Furthermore, it is not ethically viable to attain new trial data for abiraterone in people in whom docetaxel is contraindicated or unsuitable because there is no longer clinical equipoise in this setting; ADT alone is their only treatment option and abiraterone plus ADT first demonstrated superior efficacy to ADT alone over 4 years ago, with no heterogeneity in the treatment effect seen across LATITUDE or STAMPEDE.[iii]	Thank you for your comment. At the fifth appraisal meeting the committee acknowledged that evidence specific to people who cannot or should not take docetaxel is not available, so it considered the treatment effect from the whole population it its decision making. See FAD section 3.10 and 3.21.
2	Company	Janssen	Janssen are concerned that statements in the ACD, regarding the effectiveness of abiraterone in people for whom docetaxel is contraindicated or unsuitable, do not provide reasonable interpretations of the data. In Section 3.11, it states: *"Overall, the committee concluded it was not possible to say whether abiraterone was equally effective, or less clinically effective for people*	Thank you for your comments. The highlighted clinical expert statements were shared with committee prior to the fourth meeting. In response to your comment, the expert statements have also been included in the committee papers for the fifth

			for whom docetaxel is contraindicated or unsuitable." Janssen wish to re-emphasise that abiraterone has a distinctly different mechanism of action to docetaxel, so there is no biological reason why the treatment effect of abiraterone in these people would be any different to that observed in pivotal LATITUDE and STAMPEDE trials. Clinical expert statements attained before the fourth appraisal committee asked this question to aid committee decision-making. Response from the Lead Investigator of the STAMPEDE study, who has extensive experience in treating patients with abiraterone in the NHS, was "No", with further justification provided. It is unclear to Janssen why relevant expert opinion has not been referenced in the ACD or provided within the committee papers. Janssen acknowledge that the committee has retrospectively looked at subgroups to aid their decision-making on this matter, however, we are concerned that statements in the ACD, which discuss age and performance status, provide misleading interpretations of the evidence. In Section 3.11, the ACD states: *"For overall survival, abiraterone was not as effective in people 70 years and over (HR 0.94, 95% CI 0.69 to 1.29) compared with people under 70 years (HR 0.51, 95% CI 0.40 to 0.65; test for interaction p value 0.003) (James et al. 2017)."* These results are confounded by the inclusion of non-metastatic patients within STAMPEDE[iv] which are not relevant to the license indication of abiraterone. There are inevitably fewer deaths in non-metastatic patients, who are generally younger and at earlier stages of disease, so these data may be skewed to show an effect modification by age when there is none. Janssen request that this misleading and irrelevant statement is removed from the ACD or correctly contextualised in light of the confounding that exists in this analysis. We are further concerned that the Committee go on to inaccurately state that results are 'similar' in the LATITUDE trial. The p-value for interaction for age in LATITUDE was not statistically significant and therefore does not substantiate this conclusion. In Section 3.11, the ACD states: *"The committee noted a similar pattern in LATITUDE, in which the hazard ratio for overall survival for abiraterone in combination compared with ADT alone was: 0.65 (95% CI 0.50 to 0.84) for people under 65 years; 0.68 (95% CI 0.55 to 0.83) for people 65 years and over and 0.86 (95% CI 0·62 to 1·21) for people 75 years and over (Fizazi et al. 2019)."*	committee meeting. The committee noted that subgroup data should be interpreted with caution as it was based a small number of people and did not specifically reflect the population for whom docetaxel is contraindicated or unsuitable. The FAD has been amended to reflect that the subgroup data by age from STAMPEDE included people with non-metastatic disease and the LATITUDE subgroup data by age was non-significant- see FAD section 3.11.

			The p-value for interaction was 0.42 and therefore provides no evidence for an effect modification by age in LATITUDE. Janssen request for this clarification to be made in the ACD. Further, despite this discussion of age within the ACD, there is no mention of age (or more appropriately, reference to frailty) in the framework in Section 3.3. The ACD appropriately recognises that the subgroup with ECOG=2 in LATITUDE was only 40 patients and therefore should be interpreted with caution and Janssen wish to re-emphasise that, statistically, a subgroup with 40 patients is too small to ascertain difference between treatment arms or to inform statistical tests for interaction.[v] Nevertheless, in Section 3.11, the ACD goes on to state: *"The committee agreed that abiraterone appears less effective among people with characteristics shared by people who cannot or should not have docetaxel based on subgroup data."* In light of the above, Janssen do not believe this is an accurate or reasonable conclusion of the evidence. Janssen acknowledge that the framework proposed for identifying people for whom docetaxel is contraindicated or unsuitable in Section 3.3 duly recognises that many factors affect a person's ability to receive chemotherapy. It is therefore also pertinent to highlight that some factors outlined in this framework, such as poor cognition or social support, have no bearing on a person's ability to respond to treatment. As such, Janssen maintain the appropriateness of utilising existing data from LATITUDE and STAMPEDE for decision-making. In Europe, 28 countries have now reimbursed abiraterone for the treatment of people with mHSPC, 5 of which have optimised use to only those unsuitable for chemotherapy using the existing evidence base.	
3	Company	Janssen	Janssen are concerned that statements in the ACD place inordinate focus on preserving novel agents for use as subsequent therapy in mCRPC, when the clinical evidence clearly shows the most value is gained when novel therapies are used as early as possible. In LATITUDE (median follow-up 51.8 months), treatment with abiraterone plus ADT significantly prolonged median overall survival (OS) by 16.8 months compared to ADT alone.[vi] That is a four times greater survival gain when used earlier in mHSPC rather than later in mCRPC, where abiraterone can only	Thank you for your comment. The committee was aware of the larger survival benefit compared with ADT alone when abiraterone was used earlier in the treatment pathway. However, it agreed that its remit was to appraise abiraterone in the proposed indication and not to identify the best order and sequence of treatments. The wording of FAD section 3.7 has been

			extend median OS by 4.4 months compared to ADT alone. People who are contraindicated or unsuitable for docetaxel currently have a life expectancy of 3 years with ADT alone, yet they could spend these 3 years progression-free in mHSPC if treated with additional abiraterone. Nevertheless, in Section 3.4, the ACD states: *"The committee concluded that the first-choice treatment for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have. It also concluded that having abiraterone in combination at this position in the pathway limits the options for follow-on treatments for people who develop hormone-relapsed disease compared with people who have had ADT alone or docetaxel in combination."* Janssen have previously explored survival adjustments for subsequent therapies; Janssen conducted an Inverse Probability of Censoring Weighted (IPCW) analysis which adjusted for use of two novel agents and results remained consistent with the primary analysis (HR= [redacted] [95% CI: [redacted]]).[vii] An analysis exploring adjustments for cross-over from the ADT arm to receive abiraterone after the study was unblinded has also been published and results remained consistent with the primary analysis (IPCW, HR=0.62 [95% CI: 0.52-0.72]).[viii] These analyses show that adjustments for downstream therapies have no notable effect on results. This is because the impact of subsequent therapies is dwarfed by the impact of treatment in mHSPC and the significant benefit accrued in the earliest stage.	updated to reflect this.
4	Company	Janssen	Janssen are concerned that statements in the ACD regarding post-progression survival after ADT alone are not reasonable interpretations of the evidence. In Section 3.8, the ACD states: *"The clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT alone in this trial."* Clinical experts made this assertion at the first appraisal committee meeting in May 2018, while STAMPEDE was ongoing. Over two years have now passed, and such assertions are no longer reflective of the latest evidence. As demonstrated in the long-term follow-up of the STAMPEDE study, even after 8 years, there is no evidence to suggest that survival curves for abiraterone plus ADT and ADT alone converge over time to substantiate these statements. Janssen request that these statements are removed from the ACD.	Thank you for your comments. The suggested wording has been removed from the FAD. See FAD section 3.8.

5	Company	Janssen	Janssen note a factual inaccuracy. In Section 3.4, the ACD states: *"The clinical experts explained that people who have docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again for up to an additional 10 cycles in the hormone-relapsed setting. This is because the benefit of docetaxel is not exhausted when used for only 6 cycles."* Expert opinion has previously advised that, on the rare occasion that docetaxel re-challenge is used in the NHS, it would only ever be up to an additional 4 cycles in mCRPC (i.e. equating to a maximum of 10 cycles across mHSPC and mCRPC settings inclusively). It is highly unlikely that a person would ever tolerate an additional 10 cycles of docetaxel in mCRPC, having already had 6 cycles in mHSPC. Janssen request that this correction is made within the ACD.	Thank you for your comment. NHS England's Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer states that use of docetaxel upfront does not impact on the current standard of care where prostate cancer has become resistant to ADT, which should be in accordance with NICE technology appraisal 101. This recommends that docetaxel should be stopped "*at the completion of planned treatment of up to 10 cycles".* No changes to FAD made.
6	Company	Janssen	Janssen are concerned that statements in the ACD describing the comparison of abiraterone with docetaxel from STAMPEDE are misleading. In Section 3.5, the ACD states: *"Data were available for 502 people with metastatic prostate cancer in the ADT alone arm, 500 in the abiraterone-in-combination arm and 115 in the docetaxel in combination arm. A comparison between abiraterone in combination and ADT alone was prespecified in the trial protocol and a comparison between abiraterone and docetaxel was done post-hoc."* Only 342 patients contemporaneously randomised to receive docetaxel (n=115) or abiraterone (n=227) contributed to the post-hoc analysis.[ix] Within this analysis only approximately 52% (n=177)[x] would have had high-risk mHSPC. Janssen request that this clarification is made within the ACD.	Thank you for your comment. The population included in post-hoc analyses has been specified in FAD section 3.5.
7	Company	Janssen	Janssen note that several statements in the ACD incorrectly describe the time-trade off (TTO) study, which was conducted to derive an estimate for disutility associated with docetaxel treatment, as a 'survey' and Janssen are concerned that use of such terminology attempts to undermine the credibility of this study. In Section 3.17, the ACD states: *"Based on a survey commissioned by the company: the company modelled a further utility decrement for being on docetaxel." [Table 1]* and *"It sourced utility values for being on abiraterone in combination from EQ-5D results from LATITUDE and for being on docetaxel in combination from a separate survey of the general public that it had*	Thank you for your comments. The word 'survey' has been replaced with 'preference study' in line with NICE writing style. All other changes made to wording of the FAD as suggested. See FAD section 3.17.

			carried out." Whilst NICE recommends using utilities derived from patients completing the EQ-5D measure (which has societal weights), these were not available for docetaxel-treated patients at the time of submission. As such, an alternative approach was used to derive utilities/disutilities through a vignette method, in which utility values were elicited from members of the general public using a TTO analysis. Janssen request that all reference to a 'survey' in the ACD is appropriately replaced with 'time-trade off study'. To this regard, Janssen are also concerned that subsequent statements in the ACD provide inaccurate conclusions regarding the source of disutility applied for docetaxel-treated patients. *"The ERG derived the disutility value from EQ-5D data collected in STAMPEDE (whole population and metastatic subgroup). The company stated that the ERG's scenario was consistent with the results from the company's survey."* A disutility of -0.07 was derived through the TTO study and was applied in the modelling for 18 weeks whilst patients are treated with docetaxel (as per the Committee's preference). The alternative disutility of -0.02 from STAMPEDE[xi] was derived for the first full-year of the trial therefore should be applied in the modelling for the first 52 weeks of the docetaxel-treated arm. Janssen clarified that both are appropriate as long as they are applied correctly in the modelling and, as shown in the ERG erratum, both approaches give similar results. As such, Janssen request that this statement in the ACD is revised to state that results from the ERG scenario and company scenario are consistent, irrespective of the disutility source used. Janssen also note a factual inaccuracy. In Section 3.17, the ACD states: *"The committee then went on to consider evidence submitted by BUG after the appeal. This showed the results of an as yet unpublished quality of life study from STAMPEDE that focused on people with high-risk metastatic disease."* As sponsors of the STAMPEDE study, Janssen are privy to analyses of abiraterone prior to publication and this quality of life study incorporated all those with metastatic disease, not specifically focused on those with high-risk metastatic disease as the ACD infers. Janssen request that this correction is made in the ACD.	

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i Kalata P, Martus P, Zettl H, et al. Differences between clinical trial participants and patients in a population-based registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry. Dis Colon Rectum. 2009;52(3):425-437. doi:10.1007/DCR.0b013e318197d13c

ii Mitchell A, Harrison M, George D, et al. Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials. Journal of Clinical Oncology 2014 32:15_suppl, 6510-6510

iii Fizazi et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017 Jul 27;377(4):352-360.

iv James et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338-351.

v Leon et al. Sample Sizes Required to Detect Interactions between Two Binary Fixed-Effects in a Mixed-Effects Linear Regression Model. Comput Stat Data Anal. 2009 Jan 15;53(3):603-608.

vi Fizazi et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019 May;20(5):686-700.

vii Janssen Response to the Appraisal Consultation Document [ID945] -27/06/2018

viii Feyerabend et al. Adjusting Overall Survival Estimates for Treatment Switching in Metastatic, Castration-Sensitive Prostate Cancer: Results from the LATITUDE Study. Target Oncol. 2019 Dec;14(6):681-688.

[ix] Sydes et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol. 2018 May 1;29(5):1235-1248.
[x] Hoyle et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019 Dec;76(6):719-728.
[xi] Woods et al. Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-adjusted Survival, and Cost-effectiveness. Eur Urol Oncol. 2018 Dec;1(6):449-458.
[xii] James et al. Abiraterone acetate plus prednisolone for hormone-naïve prostate cancer (PCa): long-term results from metastatic (M1) patients in the STAMPEDE randomised trial (NCT00268476) – Virtual ESMO 2020 Congress presentation.
[xiii] Rush et al. Comparative quality of life in patients randomised contemporaneously to docetaxel or abiraterone in the STAMPEDE trial – ASCO GU 2019 Poster presentation.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Janssen
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	Fiona Davies
Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Janssen welcome the opportunity to comment on the appraisal consultation document (ACD) for abiraterone in newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC). Janssen are pleased to see that the Committee have recognised and agreed the need to consider separately the subgroup of patients in whom docetaxel is contraindicated or unsuitable. This is an area of great unmet need where life expectancy is no more than three years. We are, however, exceedingly concerned that the Committee's conclusions, regarding the clinical evidence for abiraterone in these people, and the respective ramifications this has for cost-effectiveness, do not provide sound basis for of the negative recommendation. The Committee's perceived uncertainty in the data supporting use of abiraterone in people who are contraindicated or unsuitable for docetaxel has led to the Committee concluding that there are no appropriate estimates for cost-effectiveness. Janssen are therefore unable to resolve cost-effectiveness concerns and such conclusions have detrimental ramifications for patient access to abiraterone which would fulfil an unmet need in this setting.	
1	Janssen are concerned that statements in the ACD, regarding data for abiraterone in people for whom docetaxel is contraindicated or unsuitable, fail to acknowledge the relevance of the evidence that is available. In Section 3.11 in the ACD it states: *"No data were presented specifically for the group of people who cannot take docetaxel."* It is not possible for Janssen to present comparative data solely for abiraterone plus ADT versus ADT alone in the group of people for whom docetaxel is contraindicated or unsuitable, nor do we believe it is reasonable for the committee to insist on this for the purposes of decision-making. As highlighted through the framework proposed in Section 3.3. of the ACD, there are many factors that determine whether a patient is suitable for docetaxel, but these were not collected as part of the LATITUDE or STAMPEDE trials and so it is exceedingly challenging to retrospectively identify a subgroup which mirrors this framework. Nevertheless, unsuitability for docetaxel was not an exclusion criterion in the LATITUDE trial, nor would it have precluded patients from enrolment to the abiraterone arm of STAMPEDE trial, after the closure of the docetaxel arm. It is therefore valid to suggest that people who would otherwise meet the framework outlined in Section 3.3, may already exist in the LATITUDE and STAMPEDE datasets. Results from LATITUDE and STAMPEDE are no less generalisable than most oncology trials and therefore Janssen are concerned that the Committee's assertion will prevent this unmet need from being fulfilled. Furthermore, it is not ethically viable to attain new trial data for abiraterone in people in whom docetaxel is contraindicated or unsuitable because there is no longer clinical equipoise in this setting; ADT alone is their only treatment option and abiraterone plus ADT first demonstrated superior efficacy to ADT alone over 4 years ago, with no heterogeneity in the treatment effect seen across LATITUDE or STAMPEDE.[1]

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2	Janssen are concerned that statements in the ACD, regarding the effectiveness of abiraterone in people for whom docetaxel is contraindicated or unsuitable, do not provide reasonable interpretations of the data. In Section 3.11, it states: *"Overall, the committee concluded it was not possible to say whether abiraterone was equally effective, or less clinically effective for people for whom docetaxel is contraindicated or unsuitable."* Janssen wish to re-emphasise that abiraterone has a distinctly different mechanism of action to docetaxel, so there is no biological reason why the treatment effect of abiraterone in these people would be any different to that observed in pivotal LATITUDE and STAMPEDE trials. Clinical expert statements attained before the fourth appraisal committee asked this question to aid committee decision-making. Response from the Lead Investigator of the STAMPEDE study, who has extensive experience in treating patients with abiraterone in the NHS, was "No", with further justification provided. It is unclear to Janssen why relevant expert opinion has not been referenced in the ACD or provided within the committee papers. Janssen acknowledge that the committee has retrospectively looked at subgroups to aid their decision-making on this matter, however, we are concerned that statements in the ACD, which discuss age and performance status, provide misleading interpretations of the evidence. In Section 3.11, the ACD states: *"For overall survival, abiraterone was not as effective in people 70 years and over (HR 0.94, 95% CI 0.69 to 1.29) compared with people under 70 years (HR 0.51, 95% CI 0.40 to 0.65; test for interaction p value 0.003) (James et al. 2017)."* These results are confounded by the inclusion of non-metastatic patients within STAMPEDE[2] which are not relevant to the license indication of abiraterone. There are inevitably fewer deaths in non-metastatic patients, who are generally younger and at earlier stages of disease, so these data may be skewed to show an effect modification by age when there is none. Janssen request that this misleading and irrelevant statement is removed from the ACD or correctly contextualised in light of the confounding that exists in this analysis. We are further concerned that the Committee go on to inaccurately state that results are 'similar' in the LATITUDE trial. The p-value for interaction for age in LATITUDE was not statistically significant and therefore does not substantiate this conclusion. In Section 3.11, the ACD states: *"The committee noted a similar pattern in LATITUDE, in which the hazard ratio for overall survival for abiraterone in combination compared with ADT alone was: 0.65 (95% CI 0.50 to 0.84) for people under 65 years; 0.68 (95% CI 0.55 to 0.83) for people 65 years and over and 0.86 (95% CI 0·62 to 1·21) for people 75 years and over (Fizazi et al. 2019)."* The p-value for interaction was 0.42 and therefore provides no evidence for an effect modification by age in LATITUDE. Janssen request for this clarification to be made in the ACD. Further, despite this discussion of age within the ACD, there is no mention of age (or more appropriately, reference to frailty) in the framework in Section 3.3.

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	The ACD appropriately recognises that the subgroup with ECOG=2 in LATITUDE was only 40 patients and therefore should be interpreted with caution and Janssen wish to re-emphasise that, statistically, a subgroup with 40 patients is too small to ascertain difference between treatment arms or to inform statistical tests for interaction.[3] Nevertheless, in Section 3.11, the ACD goes on to state: *"The committee agreed that abiraterone appears less effective among people with characteristics shared by people who cannot or should not have docetaxel based on subgroup data."* In light of the above, Janssen do not believe this is an accurate or reasonable conclusion of the evidence. Janssen acknowledge that the framework proposed for identifying people for whom docetaxel is contraindicated or unsuitable in Section 3.3 duly recognises that many factors affect a person's ability to receive chemotherapy. It is therefore also pertinent to highlight that some factors outlined in this framework, such as poor cognition or social support, have no bearing on a person's ability to respond to treatment. As such, Janssen maintain the appropriateness of utilising existing data from LATITUDE and STAMPEDE for decision-making. In Europe, 28 countries have now reimbursed abiraterone for the treatment of people with mHSPC, 5 of which have optimised use to only those unsuitable for chemotherapy using the existing evidence base.
3	Janssen are concerned that statements in the ACD place inordinate focus on preserving novel agents for use as subsequent therapy in mCRPC, when the clinical evidence clearly shows the most value is gained when novel therapies are used as early as possible. In LATITUDE (median follow-up 51.8 months), treatment with abiraterone plus ADT significantly prolonged median overall survival (OS) by 16.8 months compared to ADT alone.[4] That is a four times greater survival gain when used earlier in mHSPC rather than later in mCRPC, where abiraterone can only extend median OS by 4.4 months compared to ADT alone. People who are contraindicated or unsuitable for docetaxel currently have a life expectancy of 3 years with ADT alone, yet they could spend these 3 years progression-free in mHSPC if treated with additional abiraterone. Nevertheless, in Section 3.4, the ACD states: *"The committee concluded that the first-choice treatment for hormone-sensitive metastatic prostate cancer affects the follow-on treatments a person may have. It also concluded that having abiraterone in combination at this position in the pathway limits the options for follow-on treatments for people who develop hormone-relapsed disease compared with people who have had ADT alone or docetaxel in combination."* Janssen have previously explored survival adjustments for subsequent therapies; Janssen conducted an Inverse Probability of Censoring Weighted (IPCW) analysis which adjusted for use of two novel agents and results remained consistent with the primary analysis (HR=[redacted] [95% CI:[redacted]).[5] An analysis exploring adjustments for cross-over from the ADT arm to receive abiraterone after the study was unblinded has also been published and results remained consistent with the primary analysis (IPCW, HR=0.62 [95% CI: 0.52-0.72]).[6]

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	These analyses show that adjustments for downstream therapies have no notable effect on results. This is because the impact of subsequent therapies is dwarfed by the impact of treatment in mHSPC and the significant benefit accrued in the earliest stage.
4	Janssen are concerned that statements in the ACD regarding post-progression survival after ADT alone are not reasonable interpretations of the evidence. In Section 3.8, the ACD states: *"The clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after abiraterone in combination than after ADT alone in this trial."* Clinical experts made this assertion at the first appraisal committee meeting in May 2018, while STAMPEDE was ongoing. Over two years have now passed, and such assertions are no longer reflective of the latest evidence. As demonstrated in the long-term follow-up of the STAMPEDE study, even after 8 years, there is no evidence to suggest that survival curves for abiraterone plus ADT and ADT alone converge over time to substantiate these statements. Janssen request that these statements are removed from the ACD.
5	Janssen note a factual inaccuracy. In Section 3.4, the ACD states: *"The clinical experts explained that people who have docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again for up to an additional 10 cycles in the hormone-relapsed setting. This is because the benefit of docetaxel is not exhausted when used for only 6 cycles."* Expert opinion has previously advised that, on the rare occasion that docetaxel re-challenge is used in the NHS, it would only ever be up to an additional 4 cycles in mCRPC (i.e. equating to a maximum of 10 cycles across mHSPC and mCRPC settings inclusively). It is highly unlikely that a person would ever tolerate an additional 10 cycles of docetaxel in mCRPC, having already had 6 cycles in mHSPC. Janssen request that this correction is made within the ACD.
6	Janssen are concerned that statements in the ACD describing the comparison of abiraterone with docetaxel from STAMPEDE are misleading. In Section 3.5, the ACD states: *"Data were available for 502 people with metastatic prostate cancer in the ADT alone arm, 500 in the abiraterone-in-combination arm and 115 in the docetaxel in combination arm. A comparison between abiraterone in combination and ADT alone was prespecified in the trial protocol and a comparison between abiraterone and docetaxel was done post-hoc."* Only 342 patients contemporaneously randomised to receive docetaxel (n=115) or abiraterone (n=227) contributed to the post-hoc analysis.[7] Within this analysis only approximately 52% (n=177)[8] would have had high-risk mHSPC. Janssen request that this clarification is made within the ACD.
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Prostate Cancer UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	n/a
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The ACD, which recommended against the approval of abiraterone in newly diagnosed high-risk metastatic hormone sensitive prostate cancer, focused mainly on two key issues. Firstly, the document informs us that, at the price offered by the manufacturer to NHS England, abiraterone does not meet NICE's cost effectiveness threshold for recommendation against either docetaxel or androgen deprivation therapy (ADT), the current standard of care. Secondly, the document asserts that the benefit of abiraterone for those unsuitable for docetaxel chemotherapy is unknown. We feel there are flaws in both of these reasons for rejection.
2	While Prostate Cancer UK cannot comment specifically on the price, we are concerned that NICE has released this ACD quickly after the latest committee meeting without fulfilling an appeal point upheld by the Appeal Panel. This concerned "the committee's conclusions on cost effectiveness are opaque because it did not provide an ICER range". We recognise that the availability of docetaxel means cost-effectiveness in the whole population is challenging. However, for the group of patients unsuitable for chemotherapy, there is potential to achieve cost-effectives against ADT as abiraterone provides significant comparator clinical benefit. Given the challenges to demonstrate treatment effect in these patients, because the evidence specific to age is underpowered and there is otherwise no evidence available, it is not possible to calculate an ICER specifically for this sub-group. There is, however, a clear unmet need in this sub-group who, without access to either docetaxel or abiraterone, are denied an average additional 15 months of life. They cannot simply be denied this extensive benefit because their age, frailties and comorbidities prevent them from participating in trials with large enough numbers to provide statistically significant evidence. On this basis and to ensure their unmet need is met, the committee should use the proxy of the whole population benefit of abiraterone against ADT as the comparator. This is the means by which an ICER range can be calculated. A final price negotiation can and must then happen before NICE finalises its decision.
3	We are concerned that the Committee is requiring specific evidence of treatment effect in the sub-group of patients that are unsuitable for chemotherapy. This evidence is not available. Trial populations often consist of patients that are fitter on average than the general patient population in any given condition.[i,ii] Ordinarily this does not prevent approval for the treatment in the whole population if it is shown to be effective within a trial population, as abiraterone in this indication has been. In this instance, those patients who are unable to have docetaxel are a sub-set of the population who are more likely to not be included in trials due to their older age and potential for poorer performance status. Despite this, the Committee has seen evidence showing that the abiraterone arm of the STAMPEDE trial included some men unsuitable for chemotherapy because there was an increase in the median age of the patient population accessing the abiraterone trial arm after the docetaxel trial arm closed. This patient population also contained increased frailty characteristics because of chemotherapy ineligibility. The evidence also shows that this patient population had favourable overall survival outcomes to the docetaxel trial arm population (HR 0.59 compared to HR 0.69, respectively). Clinical experts have also said that there is no

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	biological reason for any difference in efficacy of abiraterone in chemo-suitable and -unsuitable populations, as the two treatments' modes of action are completely different.
4	The Committee recognises that one determining factor for the patients that are unsuitable for chemotherapy is older age. We have shown that this factor correlates strongly with reduced chemotherapy use in our analysis of Public Health England data. The ACD also makes clear that age alone is not the only factor, and that chemo-unsuitability is based on several factors. Despite recognising that there are numerous factors which determine chemo-unsuitability, the ACD focuses on data specific to age from LATITUDE, from a small sub-group that therefore gives high uncertainty, as a suggestion that abiraterone might be less effectives in a chemo-unsuitable population. The HR for OS for abiraterone + ADT compared to ADT alone is 0.86 (95% CI 0·62 to 1·21) for people 75 years and over. It is not possible to determine the impact of age on the effectiveness of abiraterone from a small population, especially as increasing age is associated with a greater number of co-morbidities and poorer health status - both acting as confounding factors. This should not be used as evidence that abiraterone is less effective in a chemo-unsuitable population. The Committee should instead focus on benefit in the whole trial population, which is proven with a high degree of certainty. Indeed, this has previously been accepted for this drug in the castrate resistant setting. In the COU-AA-302 study, which investigated the impact of abiraterone in chemotherapy-naïve men with metastatic castrate resistant prostate cancer, men with a performance status of 1 showed less efficacy, with a HR of 0·87 (0·65–1·16) compared to 0·79 (0·66–0·93) for men with a performance status of 0. Yet, the committee reviewed the benefit of the overall population as an indication of the treatment, and thus should take the same approach in this instance.
5	Without any other available evidence, the only way to collect data on this chemo-unsuitable sub-group would be through real-world evidence gathering, potentially from the use of abiraterone in Scotland, where it is approved, or from Wales during the COVID pandemic. However, this would place an administrative burden on the NHS. Additionally, the data would not be timely, and the cohort may still not be of sufficient size to reach statistical significance. We would also note that abiraterone was approved for the whole population for use before chemotherapy in men with castrate-resistant disease, and there is a strong likelihood that men unsuitable for chemotherapy will be accessing and benefitting from it. On this basis, there should be no reason to assume that abiraterone could not benefit these patients earlier in the pathway if whole population evidence is used.
6	By requiring more specific evidence and not applying the significant benefit of abiraterone over the standard of care (ADT) in the whole population, the Committee is setting a precedent. Other treatments in the appraisal pipeline for this indication will be unlikely to have this evidence either. They will also likely struggle to achieve cost-effectiveness in comparison to docetaxel. This has the potential to block patients unsuitable for chemotherapy from having any treatment other than ADT and will see them continue to lose out on additional months of life just because they cannot tolerate chemotherapy, despite effective alternatives existing.
7	STAMPEDE is the main trial with evidence of abiraterone's effectiveness in men with metastatic hormone-sensitive prostate cancer (mHSPC). Evidence drawn from two arms of this trial showed that, in 2013, the docetaxel arm of the trial closed but the trial continued to recruit to the ADT alone and abiraterone in combination arms (among others). This meant people recruited to the trial from this point could have included people for whom docetaxel

	was contraindicated or unsuitable, because there was an increase in the median age of the patient population accessing the abiraterone trial arm after the docetaxel trial arm closed. This patient population also contained increased frailty characteristics because of chemotherapy ineligibility. However, the Expert Reference Group (ERG) highlighted, and the Committee agreed, that this did not provide the evidence specifically for the group of patients in whom docetaxel was contraindicated or unsuitable. This was because the 2013 to 2014 data would also have included people who could have docetaxel". The ACD states regarding this point that "data specific to this group was not presented to the committee. The committee concluded that assessing data specific to the relevant population was preferred." As a trial specific to this population cannot be carried out, we are left with the data from the existing key trials: LATITUDE and STAMPEDE. We have discussed with the lead statistician from STAMPEDE the possibility of extracting only those participants unsuitable for docetaxel, using the criteria included in the ACD. Unfortunately, limitations in the data mean that it is not possible to do so. This is because the criteria for exclusion from the trial were similar to the criteria contained in the ACD, including patients with baseline neutrophil count of <1,500 cells/mm and patients with a performance status of 3 or 4 (plus only a limited number of patients with performance status 2 in the trial). Further, certain criteria such as those who might be hypersensitive to the active substance in docetaxel were not recorded for participants entering the trial. Without further evidence availability that is specific to the criteria set for the chemotherapy unsuitable population, whole population data should be used to prevent denying these patients access to a life extending treatment, now and in the future.
8	Given the previous points, the ACD therefore fails to recognise that that it is not possible to obtain the evidence of effectiveness of abiraterone "specific to the relevant [chemo-unsuitable] population". It cannot be extracted from any existing trials or generated in a new trial. The consequence is that, despite abiraterone showing good efficacy across the entire trial populations, the subset of these men for whom there is no alternative treatment will progress to hormone refractory disease more quickly. They can only access abiraterone or enzalutamide when their prostate cancer is much harder to live with and their survival benefit greatly reduced. These patients have the potential to benefit from an additional 15 months of life when receiving abiraterone while their disease remains hormone sensitive. However, this benefit decreases to 4 months of additional life when given at the metastatic castrate resistant stage of disease. As well as this shortened life, these men also lose several months with a better quality of life while disease progression is delayed.
9	*Our overall response to the ACD is to call upon the Committee to recognise the lack of their preferred evidence, and the precedent this evidence preference will have for the other treatments in this indication that NICE is appraising including enzalutamide and apalutamide. If this decision is made final, the committee is shutting the door on men in this situation ever having approved access to any treatment for their condition until they are castrate resistant when treatment benefits and quality of life are greatly reduced. We call upon the committee to recognise that the trial evidence in the full population would in any other situation be considered enough to approve the treatment, as explained in our reasoning above. The strength of the evidence of the benefit of abiraterone in the whole trial population from both LATITUDE and STAMPEDE means the committee should approve abiraterone for men with high risk hormone sensitive metastatic prostate cancer who are unsuitable for docetaxel chemotherapy, conditional upon a price agreement with NHS England that produces an acceptable ICER.*

NICE National Institute for Health and Care Excellence

Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer [ID945]

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Insert extra rows as needed

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

[i] Kalata P, Martus P, Zettl H, et al. Differences between clinical trial participants and patients in a population-based registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry. *Dis Colon Rectum*. 2009;52(3):425-437. doi:10.1007/DCR.0b013e318197d13c

[ii] Mitchell A, Harrison M, George D, et al. Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials. Journal of Clinical Oncology 2014 32:15_suppl, 6510-6510

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Abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer [ID945]

4th committee meeting (10th December 2020) - questions for clinical and patient experts

About you	
Name	Noel Clarke
Organisation	The Christie and Salford Royal Hospitals Manchester
Job title or position	Consultant Urological Surgeon Honorary Professor of Urological Oncology
Are you:	x☐ a specialist in the treatment of people with this condition? x☐ a specialist in the clinical evidence base? ☐ a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other?

1. How can people who have newly diagnosed high-risk hormone-sensitive metastatic prostate cancer and who are ineligible for docetaxel be identified? Of these people, who would be eligible for abiraterone in combination with prednisone and ADT?

   The National Prostate Cancer Audit reports from 2019 and 2020, which document all newly diagnosed prostate cancer presenting in those years show that 13 to 16% of men presenting with newly diagnosed prostate cancer have metastatic disease at the time of first presentation (www.npca.org.uk). This is in a population of between 42,000 and 52,000 cases presenting annually in England and Wales. In 2018 only 27% of the eligible men actually received Docetaxel in the primary setting and this figure only rose to 36% in 2019. In the Covid-19 era this figure has dropped precipitously and most clinicians have switched to the use of Androgen Receptor Targeting agents (ARTA's: eg Enzalutamide/Abiraterone and now Darolutamide). In the current climate it is my view that most men (estimated 70-80%) presenting for the first time with untreated metastatic prostate cancer would be suitable for such an agent and Abiraterone would be a very suitable choice for many.

2. Are there any biological reasons to expect a difference in effectiveness between abiraterone in combination and ADT alone for the chemo-ineligible subgroup compared with the whole population (LATITUDE trial)? If so, what are they?

   The criteria for inclusion in the Latitude trial incorporated specific risk characteristics which exclude up to 40% of the population presenting with M1 disease in the UK (Stampede Trial Data: Hoyle A, Ali S et al European Urology 2019). The Stampede trial also showed that "Latitude low risk" patients also benefitted from Abiraterone treatment (also in Hoyle A et al referenced above). The data support the notion that chemo-ineligible patients would benefit from Abiraterone. This data is also supported by a further report from the Stampede trial group when comparing the effects of Docetaxel and Abiraterone in similar groups of patients in the trial (Sydes M et al Annals of Oncology 2017). This latter paper showed that Abiraterone had a better PSA suppressive effect but the overall survival with Docetaxel and Abiraterone was broadly similar.

3. Would overall survival be different for those in the chemo-ineligible subgroup who had ADT compared with people in the whole population for whom abiraterone in combination is indicated (LATITUDE/STAMPEDE trials) who had ADT alone? If so, why?

   Please see my answer to 2 above. The only substantial difference I can see is that men "ineligible" for Docetaxel are likely to be slightly older and less fit in general.

4. Are subsequent treatments after a patients prostate cancer becomes hormone relapsed expected to differ for those in the chemo-ineligible subgroup who had either ADT alone or abiraterone in combination compared with the whole population for whom abiraterone in combination is indicated? If so, how? If these differ to the treatments people had in LATITUDE/STAMPEDE how would this be expected to affect the overall survival estimates?

   Early primary treatment with an ARTA such as Abiraterone has a much greater effect on long term freedom from disease and absolute survival in men with M1 disease than any form of delayed treatment when the disease has relapsed. The most recent updated data from the Stampede trial presented at the ESMO Congress in 2020 confirmed the extended benefit (75% survival at 6.5 years in Latitude "Low Risk" patients). Whilst it is less

likely that patients treated initially with an ARTA will respond as effectively to re-challenge with a similar drug when they become castrate resistant the benefit from early use far outweighs any loss of efficacy in the compound when it might be administered later on treatment failure.

5. What can be inferred from overall survival subgroup analyses from the LATITUDE trial (ECOG performance status >1 and age>75) about the treatment effect in older men or men with poorer performance status?

   In my view it is difficult to interpret these data, particularly as the Latitude trial patients had higher risk characteristics, which may well have had an adverse effect on the older population.

6. Is quality of life expected to be different for the chemo-ineligible subgroup to the whole population for whom abiraterone in combination is indicated? If so, why?

   I can see no reason why the QoL should be different for any of the patients in the differing subgroups in whom Abiraterone might reasonably be tried. Data from the Stampede and Titan trials do confirm that the QoL in patients undergoing ARTA treatment is better in general than those have=ing Docetaxel (Rush HL, et al. Oral presentation at ASCO GU Virtual 2020; abstract 14. Agarwal N, et al. Lancet Oncol. 2019;20:1518-30)

7. Is there any reason to think that the cost effectiveness results of abiraterone in combination compared with ADT alone for the chemo-ineligible subgroup would be different to the whole population for whom abiraterone + ADT is indicated and were included in the LATITUDE/STAMPEDE trials?

   I can see no reason why tere would be a difference in the QoL in these groups.

Abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer [ID945]

4th committee meeting (10th December 2020) - questions for clinical and patient experts

About you	
Name	Nicholas James
Organisation	Institute of Cancer Research
Job title or position	Professor of Prostate and Bladder Cancer Research
Are you:	☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base? ☐ a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other?

1. How can people who have newly diagnosed high-risk hormone-sensitive metastatic prostate cancer and who are ineligible for docetaxel be identified? Of these people, who would be eligible for abiraterone in combination with prednisone and ADT?

   There is no simple answer to this. In terms of hard criteria that exclude docetaxel but include abiraterone, there are very few. In terms of relative fitness where given the choice, clinicians would opt for abiraterone with a strong preference, far more. Pre COVID-19 around 25% of men received docetaxel, I would estimate that at least 50% of metastatic men would be fit for abiraterone, of whom almost all would be also fit for docetaxel.

2. Are there any biological reasons to expect a difference in effectiveness between abiraterone in combination and ADT alone for the chemo-ineligible subgroup compared with the whole population (LATITUDE trial)? If so, what are they?

1. No. Within STAMPEDE, docetaxel and abiraterone arms co-recruited from 2011-2013 when the docetaxel arm closed. From 2013-4 the abiraterone arm continued to recruit with no chemotherapy randomisation, so the chemo-fit requirement no longer applied. When the docetaxel comparisons closed, the recruitment rate rose, numbers with impaired PS increased, median age increased by 2 years, max age went from 81 to 85 (data on file MRCCTU).

   It is reasonable to assume that clinicians were now entering men who were not considered chemotherapy fit. The respective hazard ratios for overall survival

for these 2 groups were 0.69 and 0.59 respectively i.e. the hazard ratio for benefit improved when the “chemo-fitness” of the patients dropped [1].

3. Would overall survival be different for those in the chemo-ineligible subgroup who had ADT compared with people in the whole population for whom abiraterone in combination is indicated (LATITUDE/STAMPEDE trials) who had ADT alone? If so, why?

   Again, this is a difficult question to answer with no firm definition of chemo-fitness or unfitness. In general, it is likely to be older men with other co-morbidities that will fall into this category – see previous answer. These men will have a higher risk of death from other causes and hence shorter overall survival. Our data suggest that the relative benefit of abiraterone is likely to be preserved however.

4. Are subsequent treatments after a patients prostate cancer becomes hormone relapsed expected to differ for those in the chemo-ineligible subgroup who had either ADT alone or abiraterone in combination compared with the whole population for whom abiraterone in combination is indicated? If so, how? If these differ to the treatments people had in LATITUDE/STAMPEDE how would this be expected to affect the overall survival estimates?

   Patients who start with ADT are likely to get abiraterone or enzalutamide on progression and this is what we saw in STAMPEDE (LATITUDE was blinded so pts were more likely to get chemotherapy as clinicians did not know if pts had already failed abiraterone or not, STAMPEDE was open label so therefore choices more “real world”). This is unlikely to be changed by being chemo-unfit – in fact will be reinforced.

5. What can be inferred from overall survival subgroup analyses from the LATITUDE trial (ECOG performance status >1 and age>75) about the treatment effect in older men or men with poorer performance status?

   See comments above. These groups are small in both STAMPEDE and LATITUDE.

6. Is quality of life expected to be different for the chemo-ineligible subgroup to the whole population for whom abiraterone in combination is indicated? If so, why?

   Again, a complex question. Age and co-morbidity can be expected to reduce QOL compared to the whole population on average. Our QOL paper shows that

abiraterone increased QOL a little compared to baseline ADT QOL. Paper draft sent as a supporting document.

7. Is there any reason to think that the cost effectiveness results of abiraterone in combination compared with ADT alone for the chemo-ineligible subgroup would be different to the whole population for whom abiraterone + ADT is indicated and were included in the LATITUDE/STAMPEDE trials?

   Relative effects are likely to be similar – all the analyses of STAMPEDE data show very stable and consistent estimates of benefit on a range of endpoints. I am unable to say how this may affect the cost-effectiveness however. There will be QOL gains in the pre-relapse setting as noted above. There will also be QOL gains from relapsing later and from reduced skeletal events and increased survival. There will also of course be increased costs for upfront drug but reduced relapse related costs, especially from bone complications but also from not receiving an AR targeted therapy post relapse and also most likely no chemotherapy. The manuscript sent as a supporting document gives our overall HE modelling.

1. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, Attard G, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR, Investigators S: Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 377:338-351, 2017