NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD2)

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(s) separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

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

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

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

Comments received from consultees

Consultee	Comment	Response
Astellas	Many thanks for agreeing to consult further on the enzalutamide Final Appraisal Determination (FAD) as a second Appraisal Committee Document (ACD). Astellas appreciates the opportunity to provide our considered response below, comprising an executive summary, a clarification request, our response to the three ACD consultation questions, and a conclusion. **Executive Summary** • Consistent with the declared favourable benefit/risk assessment by the European Medicines Agency and the approved Summary of Product Characteristics, Astellas is of the view that enzalutamide should be recommended by NICE for all adult men with metastatic castrate-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy. • There is no proper basis for NICE to restrict the conditions of use to prior abiraterone recipients for the three reasons given below. Moreover, Astellas is troubled to have received the proposed restriction without proper notice. o Firstly, as abiraterone is also licensed for treating patients **before** chemotherapy, we believe that the recommendation is inconsistent with the declared procedure for conducting a Single Technology Appraisal (" STA"), which is designed to appraise a single product, and not to make judgments across multiple indications. Patients receiving abiraterone for **any** indication would be unjustifiably denied access to enzalutamide based on the current wording of the recommendation. o Secondly, we believe that the recommendation is not in line with the agreed final scope of this appraisal, which has been the subject of consultation with relevant Stakeholders. In any event, patients treated with abiraterone had not previously been identified by NICE as a relevant subgroup. This subgroup was not defined at the scoping	Thank you for your comment. The Committee noted that most of the comments received in response to the second appraisal consultation document opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.

Consultee	Comment	Response
Astellas (cont.)	meeting or at either Appraisal Committee ("AC") meeting, despite being proposed as a group who would welcome the opportunity to receive enzalutamide by the patient representative at the first AC meeting and by both patient and physician representatives' written responses to the first Appraisal Consultation Document ("ACD"). o Thirdly, while we do not agree with the validity of the proposed restriction by NICE, evidence is emerging to describe the positive response rate of prescribing enzalutamide in patients previously treated with abiraterone. Given that some patients within this subgroup have clinically significant responses to enzalutamide treatment, we believe that clinicians and indeed patients should be given the opportunity to access enzalutamide, given its "step change" mode of action, and administrative benefits in this final stage of the disease. Otherwise, the appraisal could not properly be characterised as evidence-based. • The current proposal to preclude use of enzalutamide from all patients who have tried abiraterone both pre- and post-chemotherapy has an effect of denying a much larger proportion of eligible patients than the previous ACD had described. This decision does not reflect the available evidence; is inconsistent with the declared NHS Constitution guiding principles and values to deliver healthcare services in the best interests of patients; and is not an appropriate decision for an STA given that it sets a complicated precedent for future appraisal of drugs which may be used sequentially with their comparators. **<u>Clarification</u>** Prior to answering NICE's specific consultation questions we would like to clarify a key concern relating to the justification of the abiraterone restriction detailed in section 4.22 of the second ACD. Specifically, we are seeking disclosure of the scientific evidence underpinning the statement as highlighted below. *4.22 On the basis of the considerations in sections 4.19–4.21, the Committee considered that the magnitude of the additional weight that would need to be assigned to the QALY benefits would justify enzalutamide being recommended as a cost-effective use of NHS resources for patients who have received 2 or more chemotherapy regimens. However, the Committee was aware that patients in this subgroup in AFFIRM had not received previous treatment with*	Comment noted. The FAD has been amended to further clarify that no patients in the AFFIRM trial had previously received abiraterone. The Committee concluded that it had not been presented with sufficient evidence to inform a conclusion on the clinical- or cost-effectiveness of the sequential use of enzalutamide after abiraterone (see sections 4.2 and 4.23 of FAD).

Consultee	Comment	Response
Astellas (cont.)	*abiraterone and the Committee had not seen evidence about the sequential use of abiraterone and enzalutamide. Because of this, the Committee agreed that the evidence it had considered for the subgroup could not be generalised to patients who had previously received abiraterone. The Committee concluded that enzalutamide could be recommended as an option for treating hormone-relapsed metastatic prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if they have not had treatment with abiraterone and the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.* In Astellas' considered assessment, no patients in AFFIRM (which is the dataset underlying the clinical effectiveness assessment) had previously received abiraterone, as it was not licensed prior to the start of this trial. Therefore, it is not clear to us the evidentiary basis for NICE to first consider this subgroup as falling within the term "two or more chemotherapy". The wording of the ACD could be interpreted as NICE classifying abiraterone itself as a chemotherapy option. However, this is not the case. Abiraterone is not a cytotoxic agent, but a hormonal one, and as such, should not be included under the term 'chemotherapy'. When Astellas presented evidence to broaden the initial recommendation for enzalutamide use in patients whose "*disease has progressed during or after 1 docetaxel containing chemotherapy regimen*" we were asking for a recommendation in patients who had received two or more courses of **cytotoxic** chemotherapy (such as docetaxel). This was the agreed scope of the STA, and there is no proper basis to extrapolate this to include a hormonal therapy. If NICE has classified abiraterone as a cytotoxic chemotherapy, then Astellas contest that this is not a satisfactory (nor is it scientifically valid) interpretation of the available evidence. **Astellas Response** Having reviewed the second ACD sent on January 21st, Astellas are pleased that NICE has recognised the value of enzalutamide in patients regardless of the number of prior chemotherapy courses which they have been prescribed. However, we have significant concerns regarding an unexpected change to the first ACD	Comment noted. The FAD has been amended to clarify that enzaluatmide was administered in AFFIRM after 1 or more cytotoxic chemotherapy regimens. Recommendations on the use of enzaluatmide after abiraterone are not included in the FAD (see sections 1.2, 3.5, 4.2 and 4.23).

Consultee	Comment	Response
Astellas (cont.)	recommendation, specifically, the restriction of enzalutamide in patients who have previously had treatment with abiraterone. **<u>Has all of the relevant evidence been taken into account?</u>** 1. Astellas believe that all of the evidence relating to the final scope of this appraisal has been taken in to account. We maintain that evidence to support sequential use of abiraterone and enzalutamide is outside of that requested in the final scope. In any event, there is no evidence to support this restriction. However, given that this has now been raised by NICE, Astellas would like share the results of several small investigator led studies looking at sequential use of enzalutamide and abiraterone. This data had not previously been shared because we considered it to be outside of the appraisal scope, and because much of the data was not available until February 2014. These studies have very small patient numbers and no control arm and as such do not offer an opportunity for a full analysis. The studies (summarised in Table 1 below) do however demonstrate that a sizable number of patients experience a PSA response when given enzalutamide after abiraterone. Astellas therefore believe that restricting enzalutamide from patients previously treated with abiraterone, denies them the opportunity to benefit from such a response. Given that enzalutamide is a clinically effective treatment option, it is consistent with the NHS Constitution to place patients in the centre of the NHS, and for doctors to prescribe what is clinically appropriate in the interests of patients under their care. Therefore, it is for the treating doctors to make an informed decision on which treatment option should be prescribed, taking account of the individual circumstances of the patients. 2. The results presented in Table 1 (not reproduced) also suggest that the differences in MoA of the drugs have not been adequately interpreted by NICE. Enzalutamide and abiraterone have different modes of action, and as such patients have been shown to respond differently to either drug. Section 4.17 describes the Committee's view that enzalutamide has "*a different mechanism of action from other anti-androgens*" and is a "*step change compared with other androgen receptor blockers*". As such, it follows that sequential use of enzalutamide following abiraterone may be an effective treatment choice, or alternative, based on the different	Comment noted. The Committee considered the additional observational evidence provided by the manufacturer in response to the second ACD, on the sequential use of enzalutamide after abiraterone. The Committee concluded that it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzalutamide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.

Consultee	Comment	Response
Astellas (cont.)	mode of action or suitability to the individual patient's needs or preferences. Again, this argument supports giving clinicians freedom to select a treatment option based on their individual patient's response and preferences, as is the case with every other currently available therapy for the treatment of mCRPC, whether it is managed through baseline prescribing or the Cancer Drugs Fund. **Table 1 - Summary of enzalutamide efficacy in patients previously treated with abiraterone** [***table provided within the response but not reproduced here***] **<u>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</u>** 3. For the reasons given above, we do not agree with the validity of restricting the clinical use of enzalutamide to patients who have received abiraterone. This restriction does not have a proper pharmacological basis, nor is it evidence based. This consideration may be borne out of NICE's misclassification of abiraterone as a cytotoxic chemotherapeutic agent, unless NICE advise us otherwise. We would also like to further discuss the implications of basing a restriction on the use of abiraterone, which is licensed for two indications. The current wording will restrict access to patients who have used abiraterone in both the pre- and post-chemotherapy settings. Moreover, without prejudice to our disagreement with the restricted conditions of use, the proposed recommendation does not provide any clarity to inform the prescribers the clinical circumstances in which enzalutamide can be prescribed. It is not clear what "*had treatment with abiraterone*" means in clinical practice. Patients may have tried abiraterone and discontinued due to tolerability, compliance or efficacy issues. Patients may therefore be denied access to enzalutamide having not had a positive response to abiraterone. As discussed before, if the guidance is intended to describe all abiraterone indications, then we are of the view that the guidance is not consistent with the agreed scope of this appraisal which had been the subject of consultation with the relevant Stakeholders, and the declared procedure for an STA.	Comments noted. See previous responses.

Consultee	Comment	Response
Astellas (cont.)	According to the published procedural guidance, the remit of an STA is to review a single drug within a single indication[1]. According to NICE's procedure, there is no basis to perform a cost-effectiveness analysis across two indications (pre and post chemotherapy), or an analysis of sequential use in the post-chemotherapy setting where it is not within the agreed scope of the STA. Such an analysis would require the identification of sequential comparators and/or the inclusion of patients from earlier in the treatment pathway. Indeed, it is procedurally unfair to do so without proper consultation and notice to Astellas. The scope of this appraisal was to review post-chemotherapy use of enzalutamide, in line with the approved therapeutic indication set out in the Summary of Product Characteristics as it underpins Astellas' legal right to market the product. The appraisal should be based upon the evidence derived from the AFFIRM trial. Therefore, provided that the patient has received docetaxel treatment prior to enzalutamide, it is beyond the remit of an STA to seek evidence on the sequential effect of enzalutamide with *any* drug used in an earlier indication as this will fall outside of the approved therapeutic indication and the evidence underlying the centralised approval.	Comment noted. Enzalutamide has been recommended in line with its marketing authorisation. See section 1.1 of the FAD. Recommendations on the sequential use of enzaluatmide after abiraterone are not included in the FAD (see sections 1.2, 4.2 and 4.23 of the FAD).
	As already explained, it is critical to understand that this restriction unjustifiably denies access to enzalutamide for a larger number of patients than were initially deemed eligible in the first ACD. In a recent press release[2], NICE offered a clarification that "*The second Appraisal Consultation Document (ACD) published last week has actually widened the population for which enzalutamide has been recommended*." This statement appears to reinforce our assertion that NICE have not considered patients treated with abiraterone prior to chemotherapy. The outcome of the appraisal could not, in our respectful view, be considered as fair and objective.	Comments noted. See previous responses.
	4. Astellas would like to understand why patients previously treated with abiraterone have drawn more attention than patients treated with other similarly indicated drugs, or other subgroups excluded from the trial design. Evidence from AFFIRM cannot inform an evaluation of efficacy of enzalutamide	Comment noted. The FAD has been amended to clarify that patients who had previously received abiraterone, or other drugs that may confound the safety and efficacy of enzalutamide were not

[1] http://www.nice.org.uk/aboutnice/howwework/devnicetech/developing_nice_technology_appraisals.jsp
[2] http://www.nice.org.uk/newsroom/features/BehindTheHeadlinesProstateCancerDrugDecisionACruelTwist.jsp

Consultee	Comment	Response
Astellas (cont.)	if used sequentially with treatment alternatives because the trial was not designed to generate this kind of data. As with a majority of clinical trials, the exclusion criteria for AFFIRM required that patients should not have had prior treatment with drugs which may confound the true safety and efficacy of enzalutamide. Patients were excluded if they received prior ketoconazole, sipuleucel-T, concurrent anti-androgen therapy, or herbal products known to affect PSA levels, and would not have received either abiraterone or cabazitaxel as neither was licensed prior to the start of AFFIRM. As such we do not understand why abiraterone has been specifically restricted in this way. We are of the opinion that this ad hoc approach to restricting the therapeutic use of an effective treatment sits uncomfortably with the European regulatory framework and the NICE health technology appraisal procedure where the decision-making should be evidence-based taking account of the clinical relevance and the external validity of the submitted study data, where the study population should be suitable for extrapolation to the population to be treated. . **<u>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</u>** 5. It appears that NICE's last minute decision (without proper notice or proper consultation) to focus on the abiraterone subgroup was taken due to cost-containment considerations if both abiraterone and enzalutamide are allowed to be used in the NHS. As sequential use was not specified in the final scope, a cost-effectiveness analysis of this scenario has not been presented, and due to the nature of data in this field, it would not have been possible to conduct such an analysis to NICE standards. The adopted approach is procedurally unfair to Astellas. This subgroup was not defined at the scoping meeting or at either Appraisal Committee meeting, despite being proposed as a group who would welcome the opportunity to receive enzalutamide by the patient representative at the first AC meeting and by both patient and physician representatives' written responses to the first ACD. Further, the committee were openly asked of any relevant subgroups of interest, with none being identified, and positive comments were made by Stakeholders regarding the omission of any restriction relating to abiraterone. 6. We strongly support providing clinicians a choice of authorised therapeutic alternatives that would be most appropriate for the mCRPC patients under their	included in AFFIRM (see section 3.3 of FAD). Comments noted. See previous responses. Enzalutamide has been recommended in line with its marketing authorisation. See section 1.1 of the FAD. Recommendations on the sequential use of enzaluatmide after abiraterone are not included in the FAD (see sections 1.2, 4.2 and 4.23 of the FAD).

Consultee	Comment	Response
Astellas (cont.)	care, taking account the patient's individual clinical circumstances. The "step change" mode of action and administrative benefits of enzalutamide should be available to all patients regardless of prior treatment, and we believe that clinicians are best placed to make such decisions based on their knowledge of, and relationship with, the individual patient. Enforcement of the current recommendation is not compatible with the NHS Constitution which places patients at the heart of the choice of treatment pathways, and prejudices mCRPC patients' rights to effective treatment options, particularly those who have received abiraterone. The policy if not corrected discriminates against mCRPC men and is incompatible with the equal treatment principle because in relation to women, clinicians have been given more clinical freedom to access to licensed cancer treatments without such "sequential restrictions", allowing them to make more appropriate choices for their patient. **<u>Conclusion</u>** In conclusion, we submit: 1. We are troubled by the late decision to restrict the use of enzalutamide to patients who have previously been treated with abiraterone without proper notice, and believe that both the remit and the scope of this STA has been exceeded. 2. The proposed restriction is much broader than the restriction proposed in the first ACD, and will deny access to enzalutamide in many more men, including those who have accessed abiraterone via the Cancer Drugs Fund. 3. The decision does not reflect the available data and hence is not evidence-based. 4. The proposed guidance is incompatible with the equal treatment principle in that prostate cancer patients do not have the same right as female cancer patients. We are aware that the introduction of this restriction has led to considerable discontent amongst Stakeholders, in part because it is not clear how this restriction	

Consultee	Comment	Response
Astellas (cont.)	is related to the evidence presented following the first ACD, in part, because Stakeholders had not previously had a chance to debate this restriction, and in part, because abiraterone is also licensed for use in patients prior to treatment with docetaxel. Astellas are committed to continuing an open and transparent dialogue with NICE to address these issues to permit timely and equal patient access to this effective treatment option with enzalutamide, and hope that the clarifications and evidence submitted above will allow us to work together and ensure that suitable guidance is given to patients and clinicians as soon as possible.	
British Uro-oncology Group (BUG)	We write in response to your ACD as titled above. We contest the inclusion of the statement regarding patient access to enzalutamide only if they have not had prior treatment with abiraterone. The ACD published in October 2013 gave no indication that this caveat would be included or furthermore was even under any consideration. We strongly question the ethics of such a proposed clause in a second ACD. The opinion of stakeholders and the role of the consultation process during the first ACD appear to have been disregarded in this instance. Publicity around the first ACD means that patients and clinicians are now waiting expectantly to have access to enzalutamide regardless of prior therapy. We would strongly urge NICE to re-consider this proposed guidance. The remit of the STA was to review post chemotherapy use of enzalutamide, with no consideration or stipulation as to other treatments the patient may have received prior to chemotherapy, as per the AFFIRM trial. If NICE starts implementing such changes in scope and limitations, this will have a huge impact on patient outcome, clinician freedom to prescribe, survivorship rates, and provision of medicines per se across all disease areas. Therefore, so long as the patient has received treatment with chemotherapy prior to enzalutamide, it is immaterial whether they may or may not have received abiraterone prior to chemotherapy. The STA seems to have subjectively focused in on one other therapy, for what can only be assumed are potential perceived cost issues. There is no robust evidence for the sequencing of drugs for the management of metastatic castrate resistant prostate cancer (mCRPC) and we are surprised that NICE has made a decision on evidence from small retrospective studies that are not Level 1 evidence. Indeed, other retrospective studies are starting to consistently show a response to enzalutamide after abiraterone in a considerable proportion of	Thank you for your comment. The Committee noted that most of the comments received in response to the second appraisal consultation document opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17,

Consultee	Comment	Response
British Uro-oncology Group (BUG) (cont.)	men in the post chemotherapy setting and this has been the experience of many oncologists in the UK. There is a strong desire amongst clinicians to have the freedom to prescribe enzalutamide in the post docetaxel setting, irrespective of previous therapies, for patients that they believe will benefit from this treatment. The current ACD from NICE would deny some mCRPC patients the opportunity for optimal therapy. This proposed ACD prejudices persons with, and all those affected by, prostate cancer. There is no precedent or ethical reason for NICE to adopt this approach. The new PPRS scheme determines that overspend of the drugs budget will be refunded by the pharmaceutical industry. It is perverse therefore that a treatment be restricted in a group of patients in whom there remains a significant unmet clinical need, and in whom there remain limited therapeutic options. We strongly urge you to remove the clause regarding abiraterone.	4.21 and 4.23 of the FAD.
Prostate Cancer UK	Thank you for inviting Prostate Cancer UK to respond to the Appraisal Consultation Document (ACD) on Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with docetaxel-containing regimen. **About us** Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do. **Prostate Cancer UK's view on the draft decision** Prostate Cancer UK is very concerned that this decision, if confirmed, will have detrimental effect on men with prostate cancer. The restriction around the use of enzalutamide is bad news for men with advanced prostate cancer who have limited treatment options. Until now, only abiraterone has been approved by NICE for men with this stage of prostate cancer. This decision complicates the situation for men who desperately need more treatment options. We therefore call on the Committee to remove this unfair, illogical restriction on the use of enzalutamide and allow men to access to every option when they are approaching the end of their lives. Furthermore, we do not believe the Committee has justified why the restriction is	Thank you for your comment. The Committee noted comments received from patient organisations and members of the public in response to the second appraisal consultation document. Most of the comments opposed the preliminary recommendation restricting the use of enzalutamide to those who have not previously received abiraterone because it was felt that this placed a significant restriction on access. The Committee acknowledged the concern of patients, in particular that more than 7000 people had signed a Prostate Cancer UK petition calling for this restriction to be removed. The Committee heard from the clinical specialist that clinicians would like to be able to offer enzalutamide after abiraterone. Acknowledging the limitations of the observational studies (see FAD section 3.20) and the uncertainty around the evidence base for sequential treatment, the Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, the Committee agreed that the observational studies were not suitable to

Consultee	Comment	Response
Prostate Cancer UK (cont.)	now proposed, when the first ACD in October 2013 did not make any reference to sequential use of abiraterone and enzalutamide. Prostate Cancer UK is pleased that NICE are proposing to recommend enzalutamide for those men who have received one or more docetaxel containing chemotherapy, but we believe the restriction around abiraterone will see fewer men benefiting from enzalutamide. As demonstrated in a recent phase III trial[i], enzalutamide has been found to prolong the overall survival of men whose prostate cancer has spread to other parts of the body (advanced prostate cancer) and has stopped responding to other hormone therapy and chemotherapy treatments by an average of 4.8 months, although we are aware that the ERG analysis says 4.5 months. Nonetheless, we view enzalutamide as a highly important treatment option for men which should be available to men whether or not they have already had abiraterone. **Impact on clinicians** Prostate Cancer UK views the Committee's draft decision as creating unnecessary confusion, which if not overturned, will place an unnecessary burden on clinicians. At the point where a man has stopped responding to hormone therapy, the clinician now has a complicated decision to make, namely risk excluding a patient from ever having enzalutamide if they think abiraterone would be beneficial, but turns out not to work or to be poorly tolerated by that patient. If the decision was confirmed by the Committee, we believe the draft decision would result in the following scenarios for patients: • Trying abiraterone pre-docetaxel (currently available on the Cancer Drugs Fund in England) before going onto chemotherapy, but being then unable to access enzalutamide. • Having chemotherapy first, then trying enzalutamide and then trying abiraterone if all else fails. • Having chemotherapy first, then abiraterone, but again excluding enzalutamide. Following publication of the ACD, we have consulted clinicians who are very concerned about the restriction will have on men. **Professor Roger S Kirby**, Director Prostate Centre	inform a conclusion on the magnitude of the effectiveness of enzalutamide after treatment with abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2 and 4.23 of the FAD.

Consultee	Comment	Response
Prostate Cancer UK (cont.)	*"[I am] pleased the drug has been approved but disappointed and perplexed that the additional condition has been applied…It is best to let individual clinicians make a decision about drugs and as the two drugs have different mechanisms of action you may get an additional response from enzalutamide even with someone who has previous experience of abiraterone."* **Professor David Neal** Clinical Director of Surgical Oncology; Professor of Surgical Oncology; Honorary Consultant in Surgical Uro-oncology, Cambridge University Teaching Hospitals NHS Foundation Trust and Senior Research Group Leader at CRUK CI. *"NICE's decision that men with advanced prostate cancer should not be given enzalutamide if they have previously received abiraterone is not in my view based on good evidence that this approach lacks effectiveness. The mechanism of action of enzalutamide (it blocks the androgen receptor) is quite different from that of abiraterone (it blocks the synthesis of androgens).* *This decision of NICE will place doctors treating these men in a position of difficulty, they are therefore more likely to start with enzalutamide as first line treatment of hormone relapsed prostate cancer, which may not turn out to be the most cost-effective approach as abiraterone comes off patent".* **Enzalutamide: 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 enzalutamide. As we stated in our response to the consultation in June 2013, Prostate Cancer UK conducted an online survey of people affected by prostate cancer to find out their opinions on enzalutamide for the treatment metastatic hormone-relapsed prostate cancer previously treated with docetaxel-containing regimen. 63 (46 who were men diagnosed with prostate cancer) people replied to the survey. Of these, 59 people (one person did not answer the question) believe it is 'very important' (53) or 'important' (6) for enzalutamide to become a treatment option available to all men for whom it's clinically appropriate. From those who responded to our survey, respondents saw the benefits of enzalutamide providing another treatment option and improving quality of life. Comments included: *"It gives an extra option when existing treatments stop working."*	

Consultee	Comment	Response
Prostate Cancer UK (cont.)	*"[Enzalutmaide] another treatment option available which has proved successful and gives hope to increase life expectancy and quality of life."* *"Anything that can extend and improve life must be a benefit."* *"Maintain a better quality of life for those who feel all else has failed."* *"Anything that gives people a better chance of a longer life with their loved ones is important."* Prostate Cancer UK believes that enzalutamide will make a significant difference to men whose prostate cancer has spread to other parts of the body and have stopped responding to other hormone therapy and chemotherapy. This treatment could make a significant difference to men by the possibility of extending their lives at a point when there are only very limited treatment options available. Currently, only abiraterone has been approved by NICE for men with this form of prostate cancer. Since the ACD was published on NICE's website, we have been asking people affected by prostate cancer to provide their views on the draft decision. We have also launched an online and paper copy petition calling for the removal of the restriction on enzalutamide only recommended for those men who have not previously been given abiraterone. The petition says: *"I call on NICE to remove its unfair restriction on enzalutamide, which would only make the drug available for those men who haven't had the drug abiraterone. The restriction will mean that men and their doctors will have to make an agonising decision about which treatment to try at an already very difficult time. Men with advanced prostate cancer should have all options open to them, especially when they are limited to very few towards the end of their lives."* We currently have had 3,494 people sign up to our petition (as of 2pm 18th February 2014), this demonstrates the strength of feeling those affected by prostate cancer have, and supports our view that the Committee must remove the restriction on the use of enzalutamide. The names of signatories to our petition can be found in Annex A. We have also heard from many people who are very angry and concerned about the proposed restriction on enzalutamide and the negative impact it will have on men and their families. Below are a selection of quotes which highlight the severity the proposed decision could have: *"I have lost a family member and a close friend to prostate cancer. We live in the*	

Consultee	Comment	Response
Prostate Cancer UK (cont.)	*United Kingdom so let's act like it and have fair rules for all! Family of victims and victims of prostate cancer would love the opportunity to extend their lives by 4 months!"* *"My Dad has advanced Prostate Cancer, diagnosed in June 2013, at 54 years old. How dare NICE restrict the medications available for us as a family to spend as much time as possible together."* *"My husband has advance prostrate cancer and was on abiraterone for 6 months, but the cancer has spread and he is now having chemo and the abiraterone was stopped, he chose to have the chemo on the understanding that enzalutamide would be available at a later time, this news has destroyed our hope as we all know this decision is down to cost, my husband loves life and has a wonderful supportive family this is so unfair and we are now thinking about moving to Scotland its bloody disgusting that this drug is not available, my husband has worked all his life the government needs to change this decision asap."* *"My husband was offered abiraterone after chemotherapy, but it only held things for about four months. My husband now only has chance of enzalutamide to hold his cancer for a few more precious months but is denied access to this on the NHS as he lives in England. Our only option is to subscribe privately which will impact obviously in our lives causing further stress to my husband."* *I was diagnosed with prostate cancer in January 2012 by the oncology department of the Royal United Hospital, Bath. The cancer was moderately aggressive and had spread to lymph nodes. Since then I have undergone docetaxel chemotherapy, palliative radiotherapy and have had a course of Abiraterone. Throughout this time I have been receiving hormone therapy and am currently undergoing cabazitaxel chemotherapy. I have been denied Enzalutamide because I have already had Abiraterone. The current chemotherapy is extremely unpleasant; enzalutamide would be much preferable, having no significant side effects. If this treatment fails there will be no further option available unless enzalutamide gets NICE approval."* *"I have just commenced a cycle of Abiraterone as my prostate cancer has become resistant to standard hormone therapy. My PSA has begun doubling from Sept 2013 when it was down to 9 and is now over 200. I discussed treatment options with my oncologist and together we opted for abiraterone as an alternative to chemo as I am a symptomatic currently those have multiple bone deposits throughout my skeleton. I was aware that this would preclude the future use of enzalutamide but having read further on this I think it most unfair that this may be denied to me and other men in the future. I am aware of the high cost of both therapies but with no chance of a*	

Consultee	Comment	Response
Prostate Cancer UK (cont.)	*cure, I can only hope that if this fails I won't have to have chemo as the only future option. I urge NICE to reconsider their position and offer hope the men like me who at best can hope for an extended quality of life."* *"My husband Kevin has advanced PC with metastatic spread and has just started on his first cycle of abiraterone. If this fails then he is facing chemotherapy. This decision by NICE to exclude access the enzalutamide for patients who have previously received abiraterone will mean he will have no further treatment choices apart for chemo. I urge NICE to lift this unnecessary restriction. I worked as a Cancer Network Director for the last 12 years of my working life and now am managing to live with cancer on a personal and daily basis. I want to longest possible time with my husband and this drug could give him that."* *"I was given abiraterone, which, after 9 months started to damage my liver and I had to came off it. At the time, enzalutamide hadn't got a UK licence and the manufacturer was giving it away, free of charge to patients for whom abiraterone had failed. That was 14 months ago and I am now fit and healthy, living an active and useful life. My PSA is between 0.5 and 0.9. I was given enzalutamide under circumstances which no longer exist and without it I would now be dead. Well done NICE. They have passed enzalutamide, but made it unusable."* *"I have advanced prostate cancer I have had 8 months of abiraterone and now I have been taken of as it has stopped working I have received two large blasts of radiotherapy to remove the cancer from my spine which has worked and now there are plans to give me chemotherapy which has you know will kill whatever immune system I have left there is no clinical or medical reason or monetary reason why I should not be allowed to receive the life saving treatment enzalutamide why is it the rest of the world is wrong and NICE is right even in Scotland allow Enzalutamide without restrictions by the way they are still British citizens paying taxes and NHS I am begging you please allow me a decent life I do not want to die suffering."* *"Abiraterone caused liver problems for me and was stopped after 2 months. Currently having chemotherapy. Please do not deny me the chance to extend my life."* *"I have been taking Abiraterone for the past few months but it no longer works - PSA shooting up. Oncologist says enzalutamide is the only alternative but he is not allowed to prescribe it. If I can find £2,700 every month I can buy it it privately. I am a pensioner - where can I find that money? Enzalutamide would keep me alive but NICE do not give a toss!"*	

Consultee	Comment	Response
Prostate Cancer UK (cont.)	*"I have advanced prostate cancer with widespread bone metastases. Presently I am pain free and live a normal life. I receive zoladex (Goserelin) three monthly injections and my next planned treatment is to receive Abiraterone. When this treatment starts to fail, I would like the option of enzalutamide to hopefully give me more time with my friends and family. Perhaps with the promise of curative vaccines on the horizon, enzalutamide could prolong my life sufficiently to avail myself of those breakthroughs."* *"My Dad, aged 56 years, has stage 4 prostate cancer. He was diagnosed on 13 April 2012 and has been, as part of a trial, on abiraterone since. The abiraterone is starting to fail and his PSA is rising. He is likely to start chemotherapy this spring. I would hate for him to be penalised and not able to benefit from enzalutamide, simply because he was willing to participate in a trial." "…the psychological impact of thinking that an avenue of possible treatment has been closed to him cannot be underestimated, on both him and on us; it is very significant. It is also possible that he would be hesitant to enter future trials, or recommend to others that they should, for fear that he/they would be penalised and, as a consequence of volunteering, be excluded from other possible treatments. I think such penalisation is intrinsically unfair."* *"My husband has metastatic prostate cancer. He is 56 years old. He has 3 children one of whom is autistic. He has been taking abiraterone for 14 months and this is now ceasing to work. He will start chemotherapy to hold back further spread of the disease in the spring. We were told that his next step would be enzalutamide and that this was producing good results. It is absolutely devastating that this will be denied to a relatively young man, particularly when it is available in Scotland and I urge you strongly to reconsider."* **Conclusion** Prostate Cancer UK believes that NICE's draft recommendation on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with docetaxel-containing regimen is unacceptable which will deny those men access to it who have previously received abiraterone. We therefore call on the Committee to remove this unfair, illogical restriction on the use of enzalutamide and allow men to access to every option when they are approaching the end of their lives.	
Royal College of Physicians on behalf of NCRI,	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to the above ACD2 consultation. We are grateful for the opportunity to comment and would like to make the following joint submission.	Thank you for your comment. The Committee noted that most of the comments received in response to the second appraisal consultation document

Consultee	Comment	Response
RCP, RCR, ACD and JCCO	We welcome the overall conclusion that enzalutamide is a cost-effective treatment for metastatic castration resistant prostate cancer patients whose disease has progressed despite prior docetaxel chemotherapy. However, restricting patient access to enzalutamide only if they have not had prior treatment with abiraterone is a new addition which was not included in the ACD published in October 2013. Developments in treatment pathways are an on-going process and to pick up on one treatment as exclusion to a subsequent treatment is neither wise nor desirable. We would suggest that so long as the patient has received treatment with chemotherapy prior to enzalutamide then they should have the option of access to enzalutamide, if clinically appropriate, irrespective of whether they may or may not have received abiraterone prior to chemotherapy. Whilst the optimum sequencing of treatment strategies in metastatic castrate resistant prostate cancer (mCRPC) remains to be determined, our experts do not believe it is prudent to base decisions on small retrospective series. Some retrospective series have suggested partial cross-resistance and equally some have suggested response rates of 38% [1] in this group of patients who have previously received abiraterone and docetaxel chemotherapy. Therefore, in the absence of any robust evidence, we believe that the restrictive clause in the current ACD from NICE is open to challenge and has the potential to compromise patient care with resultant implications on survival rates. At the very least, it would deny some men the option of the only effective therapy for their stage of disease in progressive MCRPC. Despite significant progress in management of mCRPC there still remains a dearth of effective treatments in this setting and enzalutamide provides an effective treatment option with significant clinical benefits. We would therefore strongly recommend the removal of the restrictive clause regarding abiraterone treatment as an exclusion factor for subsequent enzalutamide.	opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.
Tackle Prostate Cancer	On behalf of The Prostate Cancer Support Federation (please note our new working name, "**Tackle prostate cancer**") I am writing to give the response to the above ACD Tackle, whilst pleased that enzalutamide has been passed for use, is dismayed that a caveat has been introduce which precludes its use after Abiraterone. We believe that the insertion of this caveat is unfair, is in contravention of the very sound procedures NICE created to avoid such situations and also is not based on any	Thank you for your comment. The Committee noted that most of the comments received in response to the second appraisal consultation document opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical

Consultee	Comment	Response
Tackle Prostate Cancer (cont.)	sound evidence. ***Has all of the relevant evidence been taken into account?*** **No** It would appear that introduction of the caveat is based on a very small study involving only 35 men (see http://www.ncbi.nlm.nih.gov/pubmed/23849416). Even in this, it is stated that "a small but significant number of patients showed significant benefit from sequential treatment". NICE legitimately pride themselves on only considering level 1 phase 3 randomised trial evidence but on this occasion a decision is being made on a few anecdotal retrospective studies. This is grossly inconsistent; we need to wait for randomised sequencing studies before making any judgement on the order of therapies. Clinical experience, of just as good quality, shows that enzalutamide can work after abiraterone and this ruling will restrict a significant number of men from effective therapy. It has been estimated from the CDF that around 3000 will be treated with pre chemotherapy abiraterone and this has major implications on further therapy for them. In my own case, in December 2012, I was given enzalutamide after it was found I could not tolerate the liver damage abiraterone was causing. Thirteen months later, I now live a totally normal and productive life, with a PSA of around 0.5. I help to run the Tackle support line and I have had men (and women) in tears on the phone to me about the death sentence that NICE have given them. ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** ***NO*** In October 2013, an ACD was circulated which approved the use of enzalutamide for hormone relapsed disease with a two caveats, namely that the patient should have undergone exactly one course of chemotherapy (docetaxel) and the manufacturer offered a discount. This was based on a reasonable interpretation of the evidence presented to the committee and discussed in public, and on the strength of it, a significant number of men who were failing with abiraterone and therefore facing imminent death were informed by their oncologists that relief was at hand and that enzalutamide would be available for them in the New Year. The subsequent insertion of the caveat regarding abiraterone dashed these men's hopes.	evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.

Consultee	Comment	Response
Tackle Prostate Cancer (cont.)	We understand that the process of assessing a treatment is long, and that drafts of the results are subject to change, but change is only justified if new evidence comes to light, which is not the case here. It may be that the committee felt that there was something that they had overlooked and it was this that prompted them to introduce this caveat. In issuing the first ACD NICE placed itself on record as having no reservations about the effectiveness of enzalutamide after abiraterone had failed. We think it not right to go back on that position without new evidence. To do so would be against the principles that NICE has set itself When Abiraterone has been given, the cost to the NHS has been budgeted. As Enzalutamide is much the same price as Abiraterone, the cost to the NHS would not be any more than has already been allowed for in the budget. If the patient does not respond to Enzalutamide, it will be apparent very quickly and treatment will be stopped. Therefore, the cost to the NHS will not be great. ***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*** ***No*** We are concerned that well established procedures have not been followed in two significant ways, and this makes the recommendation unsound and unsuitable. First, a major caveat was introduced without discussion, and secondly, there is nothing in the STA process that allows consideration of these other factors. On the first point there is little more to be said; the caveat was not discussed at the consultation meeting and no sub groups were initially considered. The second point is more recondite. In adding the caveat, the Commitee were acting outside their scope, which was to consider the role of enzalutamide in the post chemotherapy setting. The use of previous therapies is outside their remit and should not be included. Thus an arbitrary decision has been made without any data. (To illustrate this it is worth considering a patient's previous treatment history; it may be that response to enzalutamide differs depending on the primary treatment and subsequent androgen deprivation regime adopted, but there is no evidence what this might be. In making its decision regarding previous use of abiraterone the committee is behaving in the same way as it would have been if it decided that enzalutamide should only be used for zoladex treated men, and not those who had prostap.	

Consultee	Comment	Response
Tackle Prostate Cancer (cont.)	The caveat takes away all clinical freedom for clinicians who aim to maximise therapy for individual patients. Any exclusions should be considered at local level on an individual patient basis. Such a caveat has never been applied for other drugs where they have been considered on the merit of their licence and not as part of the overall prescribing pathway. We would like to find with NICE a resolution that is agreeable to both parties. It would be very sad if we had to escalate the issue and formally appeal against the Final Assessment Document if this caveat is not removed. We would, as is our right as the voice of patients, appeal against the recommendation on 3 grounds: 1. it is unfair on men who were, last October, led to the reasonable belief that enzalutamide would soon be available; 2. the process by which the caveat has been introduced is not in accordance with NICE's procedures; 3. the evidence on which they seem to base the caveat is well below the standards normally expected by NICE	

Comments received from commentators

Commentator	Comment	Response
Janssen	Please find below Janssen's response to the revised Appraisal Consultation Document (ACD) for enzalutamide issued in January 2014. We are pleased to have an opportunity to provide our comments in relation to the interpretation of the cost-effectiveness evidence and reiterate our support for NICE to make additional treatment options available to patients with mCRPC. 1. The rapid approval of several novel agents in recent years has given prostate cancer patients and their treating physician new and effective therapeutic options. With the rapid introduction of these agents to routine clinical practice, questions will inevitably arise about their optimal sequencing in the context of existing therapies, with further evidence needed to fully define how best to use these agents, in which patients and in which sequence.	Thank you for your comment. The Committee noted that most of the comments received in response to the second appraisal consultation document opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee

Commentator	Comment	Response
Janssen (cont.)	Overall, there are no robust data currently available that could determine the appropriate sequencing of the newer agents approved to treat mCRPC, particularly since the clinical trials investigating these agents were completed in a very quick timeframe and the development programs overlapped one another. In the absence of this, the choice of which NICE-approved agent to use in a patient should be determined by individual clinicians based on clinical need and efficacy. According to the draft decision by the National Institute for Health and Care Excellence (NICE) released on 28th January 2014, NICE is consulting on a proposal to recommend enzalutamide in men with metastatic castration-resistant prostate cancer who have been treated with docetaxel, but who have not yet received prior treatment with abiraterone. i. This decision puts clinicians and patients in a difficult situation as they are being faced with a very difficult dilemma. As well as having to select which treatment will work better for a particular patient, they do so knowing that if they opt to prescribe abiraterone, they are ruling out the possibility of prescribing enzalutamide later on. Likewise, the guidance could inadvertently be misinterpreted to mean that abiraterone is allowable after enzalutamide, but not vice versa. This would cause sequencing by default, which is exactly what the ACD was seeking to avoid. ii. Our concern is that incorporating such a statement into the guidance would be prejudicial against Janssen. The guidance as currently worded creates a natural inequity against abiraterone acetate simply because of the timing of the appraisals and risks Janssen being disadvantaged purely for being first to market. This is because there is no mention of enzalutamide in NICE's abiraterone guidance (as one would expect as enzalutamide was not licensed at the time of issue), but abiraterone is referenced in the enzalutamide guidance. The unintended consequence of this may be to infer that physicians should use enzalutamide first followed by abiraterone. We have already seen evidence of this interpretation in some units following enzalutamide's similar approval on the National Cancer Drugs Fund. iii. Thirdly, this is a move that limits patient access through the introduction of unnecessarily restrictive wording that compounds a situation in which treatment options are already limited at this stage of the patient	agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.

Commentator	Comment	Response
Janssen (cont.)	pathway. 2. In our initial response to consultation, we highlighted two key points in relation to the following: i. The indirect comparison presented by the manufacturer does not utilise the most comparable datasets (Section 3.11, 3.12 and 3.18 of the ACD) ii. Assumptions made by the manufacturer about the HR for OS and treatment duration in the economic analysis are subject to significant uncertainty (Sections 4.9 and 4.10 of the ACD) We note that whilst the committee acknowledged the concerns that were raised in relation to time-dependency and potential bias against abiraterone, the proposed solution of using more mature datasets does not explicitly address the shortcomings in the manufacturer analyses (Janssen response to consultation November 2013). In this regard, particularly around the comparability of the datasets used and differences between the trials, we would like to reiterate our initial concerns documented in our original response to the first enzalutamide ACD in November 2013. We note that a number of clinical experts (in the manufacturer's own words) believe that enzalutamide and abiraterone have the same clinical effect (page 25). Given that the manufacturer's indirect comparison showed no statistically significant difference for overall survival (page 36), the potential inference from the ACD that enzalutamide is superior to abiraterone is a gross misinterpretation of the evidence presented by Astellas and somewhat misleading, if not wholly inaccurate. We propose that necessary caveats are introduced explicitly in the revised ACD to highlight the fact that, whilst the point estimates in the indirect comparison presented to the committee suggest a difference in treatment effect between enzalutamide and abiraterone, this difference is not substantiated either clinically or statistically.	Comments noted. The Committee considered all available evidence and the level of uncertainty around all analyses during the course of the appraisal.

Summary of comments received from members of the public

Theme	Response
NICE received a large volume of comments from members of the public. Most of the comments opposed the restriction on the use of enzalutamide to those who have not previously received abiraterone.	The Committee noted that most of the comments received in response to the second appraisal consultation document opposed restricting the use of enzalutamide to those who have not previously received abiraterone. The Committee noted comments from the manufacturer and professional organisations acknowledging the absence of robust clinical evidence on the most effective sequencing of enzalutamide and abiraterone. The Committee heard from the clinical specialist that in clinical practice, clinicians would like to be able to offer enzalutamide after abiraterone. The Committee agreed that a proportion of patients may benefit from treatment with enzalutamide after abiraterone. However, it had not been presented with sufficient evidence to inform a conclusion on the magnitude of the effectiveness of enzalutamide after abiraterone. Therefore, it could not make recommendations on the sequential use of enzalutamide and abiraterone. The Committee concluded that recommendations for enzalutamide could be developed only for people with metastatic hormone-relapsed prostate cancer whose disease progressed on or after docetaxel therapy (in line with the marketing authorisation for enzaluatmide). For further details, see sections 1.1, 1.2, 4.2, 4.17, 4.21 and 4.23 of the FAD.

[i] [i]Increased survival with enzalutamide in prostate cancer after chemotherapy. Scher, H et.al. The New England Journal of Medicine. September 2012.