

## **Single Technology Appraisal**

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

## **Committee Papers**

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

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

**Contents:**

The following documents are made available to consultees and commentators:

1. [Appeal Panel Decision](#)
2. [Evidence Review Group critique of post-appeal data](#)
3. **The following papers were submitted by the British Uro-Oncology Group (BUG), Prostate Cancer UK and Tackle Prostate:**
  - a. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial [published correction appears in Ann Oncol. 2020 Mar;31(3):442]. Ann Oncol. 2019;30(12):1992-2003.
  - b. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338-351.
  - c. Hoyle AP, Ali A, James ND, et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019 Dec;76(6):719-728.
  - d. 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). ESMO Virtual Congress, 2020
  - e. Fizazi K, Tran N, Fein L, 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.
  - f. Cost-effectiveness analysis paper on abiraterone plus ADT versus ADT alone for newly diagnosed advanced prostate cancer, based on data from the STAMPEDE trial. Including results for those with metastatic disease at baseline.
  - g. Paper on the quality of life (QLQ-C30) for men with prostate cancer contemporaneously randomly allocated to receive either docetaxel or abiraterone in STAMPEDE

These papers have either been published in journals or are being prepared for publication. The papers were seen by the Committee but since they are either under copyright or are academic in confidence we cannot include them in these papers.

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

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE  
SINGLE TECHNOLOGY APPRAISAL  
APPEAL HEARING**

***Advice on abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer [ID945]***

**Decision of the Panel**

**Introduction**

1. An Appeal Panel was convened on 3 September 2020 and 4 September 2020 to consider an appeal against NICE's final appraisal document, to the NHS, on abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer [ID945].

2. The Appeal Panel consisted of:

- Professor Jonathan Cohen      Chair
- Sharmila Nebhrajani      NICE Chairman (Non-Executive Director)
- Dr Biba Stanton      Health Service representative
- Uday Bose      Industry representative
- Colin Standfield      Lay representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Panel considered appeals submitted by Prostate Cancer UK and Tackle Prostate Cancer (PCUK/TPC; the charities), the British Uro-Oncology group (BUG) and Janssen (the company).

5. Prostate Cancer UK and Tackle Prostate Cancer were represented by:

- Heather Blake      Director of Support and Influencing, PCUK
- Karen Stalbow      Head of Policy, Knowledge and Health Information, PCUK
- Rebecca Leszczynski      Senior Knowledge Officer, PCUK
- Dr Steven Allen      Patient Representative, TPC
- Robert Horsley      Patient Representative, PCUK

6. The British Uro-Oncology Group was represented by:

- Professor Nicholas James STAMPEDE Trial Chief Investigator

7. Janssen was represented by:

- Amanda Cunnington Director of Health Economics, Market Access, Reimbursement (HEMAR) and Patient Engagement & Government Affairs
- Dr Adela Williams External Legal Counsel
- Mohamed Lockhat Therapy Area Medical Director – Oncology
- Fiona Davies Senior HEMAR
- Nicola Trevor HEMAR Lead

8. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:

- Professor Amanda Adler Technology Appraisal Committee B Chair
- Helen Knight Programme Director, NICE
- Dr Nick Latimer Technology Appraisal Committee B member
- Dr Sanjeev Patel Technology Appraisal Committee B member
- Ross Dent Associate Director, NICE

9. The Appeal Panel's legal adviser Stephen Hocking (DACBeachcroft LLP) was also present.

10. Under NICE's appeal procedures members of the public are admitted to appeal hearings and several members of the public and NICE staff observed the proceedings which were held via Zoom.

11. There are two grounds under which an appeal can be lodged:

Ground One: In making the assessment that preceded the recommendation, NICE has:

- a) Failed to act fairly
- b) Exceeded its powers.

Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.

12. The Vice Chair of NICE (Mr Tim Irish) in preliminary correspondence had confirmed that:

- Prostate Cancer UK and Tackle Prostate Cancer (PCUK/TPC) had potentially valid grounds of appeal as follows: Grounds 1a and 2
- The British Uro-oncology Group (BUG) had potentially valid grounds of appeal as follows: Grounds 1a and 2

- Janssen had potentially valid grounds of appeal as follows: Grounds 1a, 1b and 2
13. The numbering of appeal points in this letter reflects those used at the hearing. In places these may appear not to be chronological because of points not taken forward after the scrutiny stage (e.g. there is no Janssen 1a5). Further, the order in which points were presented at the appeal hearing is not the order of this letter and appellants and the Committee cross referred to their earlier submissions while addressing later points. The summary of submissions made below is not intended to be a verbatim account of what was said at the time each point was discussed, but a brief summation of the appellant and Committee submissions relevant to each point as they emerged during the whole hearing.
  14. The appraisal that is the subject of the current appeal provided advice to the NHS on abiraterone for treating newly diagnosed metastatic hormone-naïve prostate cancer.
  15. Before the Appeal Panel inquired into the detailed complaints the following made a preliminary statement: Heather Blake on behalf of PCUK, Prof Nicholas James on behalf of BUG, Amanda Cunnington on behalf of Janssen and Professor Amanda Adler on behalf of the appraisal committee.
  16. Mr Robert Horsley gave a patient testimony, describing his own experience of treatment with abiraterone for metastatic prostate cancer.
  17. In the appeal hearing, and in this letter, references to “men” should be understood to include a person of any gender who has or may suffer from newly diagnosed metastatic hormone-naïve prostate cancer.

### ***Appeal by Prostate Cancer UK and Tackle Prostate Cancer (PCUK/TPC)***

**Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly.**

**PCUK/TPC Appeal Ground 1a.1:** In making the assessment that preceded the recommendation, NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.

18. Heather Blake, for PCUK, stated that the Committee had not tried to identify and make a recommendation for men who were ineligible for or who would not take chemotherapy. Such a group clearly existed. Those men tended to be older, and to have more serious comorbidities. PCUK had performed an analysis demonstrating disparity in access to chemotherapy relating to age. 63% of men under 70 would receive chemotherapy. In contrast, 22% of men over 70 and only 5% of those over 80 would. Older men also tended not to take up radical prostatectomy.
19. She said that these differences could not be attributed to patient choice. Patients could only be forgoing the life extending benefits of chemotherapy because of valid physical reasons outside the patients’ control. Mr Horsley was an example of someone who, if he were not receiving abiraterone exceptionally because of

temporary commissioning policies put in place as a result of the COVID-19 pandemic, would have been left without a substantially life-extending treatment.

20. Rebecca Leszczynski, for PCUK, responded to an earlier assertion by NICE that the hazard ratio (HR) for men over 70 was 0.94 with a wide confidence interval crossing 1 by saying that the wide confidence interval was probably an artefact caused by the small number of cases. In STAMPEDE after recruitment to the docetaxel arm had closed an improved hazard ratio of 0.59 was seen, but the mean age of the patient population had increased. In LATITUDE the hazard ratio for overall survival remained favourable for the over 65s (comparison with ADT) and remains 0.86 for the over 75s (admittedly with a wide confidence interval).
21. Professor James, for BUG, said that he agreed with PCUK. He added that a failure to provide abiraterone discriminated not just on grounds of age but also against men of African or Asian origin (the former being more likely to get prostate cancer, the latter having a typically worse prognosis when they do, than men of white origin). Professor James confirmed PCUK's assertion that STAMPEDE provided support for an improved HR in older patients. He said that STAMPEDE had good quality of life data and NICE knew this: in his view, the failure to obtain the data had resulted in discrimination.
22. Professor Adler, for the appraisal committee, explained that this was largely a legal point and the Committee was without legal representation. She said that committees avoid making recommendations based on age, race or gender. In general subgroups are avoided if a drug is effective in a whole patient population. In this case, it is comorbidities and frailty, rather than age per se, that affects access to docetaxel. She said that if committees were to increase ICER thresholds for older people they would have to reduce thresholds for other groups (e.g. children). In this case, even with the assumption that abiraterone is equally effective in chemo-unfit men, abiraterone was not cost-effective compared with ADT alone.
23. Ross Dent explained that in this appraisal stakeholders were asked to comment on equality issues at the scoping stage, when they made their submissions, and in consultation. No comments were received during consultation saying that NICE had missed anything or that the draft recommendation had equality impacts. The Committee knew that two thirds of men received ADT alone and so ADT was a relevant comparator, but so was docetaxel. In fact, the Committee did look at cost-effectiveness for people who have ADT alone, but the treatment was insufficiently cost-effective in this group. Professor Adler agreed.
24. Heather Blake responded that PCUK had highlighted men who could not receive docetaxel in its response to consultation. Karen Stalbow added that the charities had initially focused on unmet need and initially dealt with the whole patient population, but became more focused on the docetaxel ineligible population from July 2019. There was a large population of men who could not get the life extending benefits of docetaxel and this was clear indirect discrimination.
25. Professor James added for BUG that the end point for the trials was overall survival. As men age then other causes of death become more important and the effect of

prostate cancer is “diluted”. Therefore progression free survival (PFS) was a better measure of effectiveness. The effect on PFS was very similar in older and younger men and being kept symptom free was an important benefit. He was not requested to release his data by NICE.

26. Dr Nick Latimer, for the appraisal committee, responded that the Committee accepted older men were more likely to be chemo unfit but there was no age analysis provided specific to the chemo unfit population. The Committee did look at a population that did not take docetaxel and the ICERs in this group were much too high. A recommendation would have displaced other more cost-effective treatments for other populations.
27. Karen Stalbow, for PCUK, said there was a failure by the Committee to identify a population who would not receive docetaxel. PCUK had tried to respond with evidence. They had responded as quickly after the January 2020 meeting as they could.
28. The Appeal Panel concluded as follows. The Panel has concluded below (paragraph 89) that the Committee should have undertaken further work to explore the possibility of defining a subgroup of patients who are unable or unlikely to receive docetaxel, and that its reasoning around why it has not yet done so was not sufficient. As part of that conclusion, the Panel also finds that the current reasoning around the failure to define this subgroup does not address the fact that the subgroup will tend to comprise older men. This amounts to not having “due regard” to the impact of not recommending treatment for this group, or alternatively to the possibility of advancing equality by making a positive recommendation for the group. It was unfortunate that this issue was not raised by consultees in response to a specific question about equality impacts during consultation on the ACD, but the Panel felt that the issue was sufficiently clear that in this case the Committee should have proactively identified and discussed it.
29. However, the Panel makes no finding on whether, once this subgroup has been more thoroughly considered, it might be discriminatory not to make a positive recommendation for them. Any finding on that point would be hypothetical at this stage. However, the Panel wishes to be clear that although equality legislation requires this subgroup to be more fully considered it does not necessarily follow that in this case, after appropriate consideration, special provision will need to be made for them. These are two distinct steps, and the need to ensure that NICE recommends only cost-effective treatments is also an important and legitimate consideration, to be weighed alongside any consideration of equality.
30. The Appeal Panel therefore upheld the appeal on this point. Despite the fact that this was not specifically raised by the appellants during the consultation process, the Institute must have in mind the fact that older men are over-represented in the chemo-ineligible subgroup when it considers the possibility of defining and making a recommendation for this subgroup.



## ***Appeal by the British Uro-Oncology Group (BUG)***

**Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly.**

**BUG Ground 1a.1:** Related to BUG's points 2 and 8, which is that the Committee failed to act fairly by not requesting and/or not considering the STAMPEDE group's recent cost-effectiveness analysis referred to in the appeal letter.

31. Professor James, for BUG, stated that the STAMPEDE group have large amounts of data that could have been used by NICE for modelling. They have now conducted their own modelling, using disease states rather than line of therapy. He argued that this is more appropriate than the model used by NICE. He expressed surprise that NICE modelling showed an ICER considerably higher than the cost-effective range, as their modelling shows an ICER of £20,000-30,000 with a 50% discount on the cost of the drug. He said that it was unfair for NICE not to ask to obtain this data directly from the STAMPEDE group.

32. Professor Adler, for the appraisal committee, emphasised that NICE processes put the onus on the company to submit data to NICE for the economic model. As discussed, under BUG 1a2, the Committee recognised the potential usefulness of obtaining additional data from STAMPEDE, particularly on Quality of Life (QoL). They had indeed requested this information, but it had not been provided.

33. Dr Nick Latimer, for the appraisal committee, thought that Professor James may have misunderstood an aspect of the modelling. Whilst the cost side was based on line of therapy, the effect side was not.

34. The use of QoL data from the STAMPEDE trial is discussed in more detail under BUG 1a2 below.

35. With regard to the specific issue of BUG's recent cost-effectiveness analysis, the Appeal Panel concluded as follows. The Panel noted that this analysis was presented in February 2020, after the final meeting of the appraisal committee in January 2020. The Panel noted that, according to NICE processes, the cost-effectiveness analysis in an appraisal is based on the company model as critiqued or amended by the Evidence Review Group. Consultees also have the opportunity to highlight additional evidence in their response to consultation. In this case, the Panel judged that NICE had followed its processes fairly and taken reasonable steps to obtain the necessary evidence for this appraisal.

36. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal Ground 1a.2:** Related to BUG's point 9, which is that that the Committee failed to act fairly by not requesting and/or not considering the STAMPEDE group's recently presented quality of life data referred to in the appeal letter.

37. In their appeal letter, BUG said that they had recently presented comparative quality of life data from men contemporaneously recruited to the STAMPEDE docetaxel and

abiraterone comparisons showing persistent gains on Quality of Life (QoL) for abiraterone over docetaxel out to two years post randomisation.

38. In their response to initial scrutiny, they said that the prolonged duration of this appraisal meant that highly relevant information could have been available to the Committee had they asked for more evidence in the more recent meetings.
39. At the appeal hearing, Professor James, for BUG, explained that he was the Chief Investigator of the STAMPEDE trial, run by the MRC Clinical Trials Unit at University College London. He said that NICE should have asked the STAMPEDE investigators directly for access to their QoL data. Although this data was presented at a conference only in February 2020 (after the final meeting of the appraisal committee) it had been on file for some time. He explained that it can be difficult for pharmaceutical companies to negotiate access to data from publicly funded trials but said that the investigators would have shared this data with NICE if they had been asked for it directly.
40. Professor Adler, for the appraisal committee, explained the Committee was aware that the STAMPEDE trial had collected QoL data using their preferred measure (the EQ5D) on patients treated with abiraterone, docetaxel and androgen deprivation therapy (ADT) alone. Over the course of the appraisal, the Committee repeatedly expressed a preference for these data over those provided by Janssen in their submission. Despite this, Janssen had not obtained these data to submit to the Committee.
41. Fiona Davies, for Janssen, said that the company had also appreciated the relevance of this data from STAMPEDE. They had tried to negotiate access to this, but they had been unable to reach an agreement with the MRC/University College London.
42. Helen Knight, for NICE, said that according to NICE processes, the principal source of evidence in all appraisals is the company. Other relevant stakeholders are allowed to submit evidence, but the onus is on the company to provide information. During the consultation stage, all stakeholders are asked to comment on whether all relevant evidence has been considered. The MRC were therefore given the opportunity to alert NICE to additional evidence and provide this.
43. In response to a question from the Panel, Ms Knight went on to say that NICE can facilitate access to data if companies are struggling to obtain this. She stated that in this case, NICE were not made aware that Janssen were struggling.
44. Dr Adella Williams, for Janssen, said this was not correct and offered to provide email correspondence from Janssen to NICE regarding their attempts to negotiate access to the STAMPEDE data. These emails were subsequently provided to the Appeal Panel.
45. Professor James, for BUG, said that BUG would have had an opportunity to comment on this issue if the second Appraisal Consultation Document (ACD) had been published.

46. The reason that the Committee prepared a second ACD that was not shared with all stakeholders was discussed under another appeal point at the hearing. Ross Dent said that they were trying to help to facilitate the protracted commercial negotiations between NHS England (NHSE) and the company by providing the company with their preferred modelling assumptions. They produced a second ACD and a list of their preferred assumptions. The latter was shared with Janssen but not other stakeholders. The second ACD was not circulated for formal consultation.
47. Later in the hearing, Ross Dent, for NICE, said that colleagues at NICE had in fact contacted UCL about access to STAMPEDE data, so UCL were aware that they could submit this data to NICE for the purposes of the appraisal. Following the hearing, the Appeal Panel were provided with this email correspondence between NICE and MRC/UCL.
48. The Appeal Panel concluded as follows. The Panel accepted that NICE processes put the main onus on the company to provide evidence for the appraisal, and also provide opportunities for other stakeholders to submit additional evidence. The Panel noted the Tameside Duty on public bodies to take reasonable steps to obtain the necessary evidence before reaching a conclusion.
49. In this case, the appraisal committee clearly stated that they wanted to access QoL data from the STAMPEDE trial. It is clear that Janssen did try to obtain this from the MRC/UCL but these negotiations were not successful, so Janssen could not submit this data to NICE. From the email correspondence between NICE and the MRC/UCL it is also clear that NICE made efforts to facilitate access to this data but these also seem to have been unsuccessful.
50. Consultees had the opportunity to highlight additional evidence in their response to the first ACD. The Panel noted BUG's concern that they had not had a chance to respond to the second ACD and agreed that in general it is expected that all consultation documents will be shared with all stakeholders. However, the Panel recognised that NICE had prepared the second ACD with a specific aim of facilitating the protracted commercial negotiation between Janssen and NHSE. Given that the recommendations in the second ACD were unchanged from those in the first ACD, the Panel did not find that the failure to share the second ACD with all stakeholders constituted unfairness.
51. The Panel judged that the Committee had taken reasonable steps to obtain the necessary evidence for this appraisal and provided a fair opportunity for consultees to highlight additional evidence at consultation.
52. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal Ground 1a.3:** That the failure of the Committee to consider the STAMPEDE group's recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision.

53. The discussion of this appeal point is summarised under PCUK point 1a.1 above.

54. The Appeal Panel concluded as set out under PCUK 1a.1 above.

55. The Appeal Panel therefore upheld the appeal on this point.

**BUG Appeal Ground 1a.4:** Related to BUG's point 10, that the Committee failed to act fairly by not taking into account COVID-19.

56. Professor James, for BUG, said that the COVID-19 pandemic is an unprecedented event, which may have changed the healthcare landscape forever. The FAD for this appraisal was issued in June 2020, at the height of the pandemic. Although the final Committee meeting was in January 2020, there was the opportunity for NICE to add an urgent addendum to its guidance between January and June. He explained that the risk of death from COVID-19 is higher in men, black and minority ethnic (BME) groups and those who are overweight: these are also risk factors for death from prostate cancer. Docetaxel treatment requires hospital visits, and causes immunosuppression. BUG wrote to NHSE to point out the additional benefits of abiraterone over docetaxel in the context of the pandemic, and NHSE responded quickly to make abiraterone available during this period. Professor James said that we are now in a situation of endemic COVID-19 so it is likely that these additional benefits will continue to be important.

57. Dr Sanjeev Patel, for the appraisal committee, reiterated the timeline. The final Committee meeting was on 15/01/2020. The first imported cases of COVID-19 in the UK were reported on 29/01/2020. WHO declared a pandemic on 11/03/2020. The NHS issued guidance on cancer treatment on 20/03/2020 and the FAD was issued on 26/06/2020.

58. Helen Knight, for NICE, explained that the technology appraisal programme had taken advice at the start of the pandemic and was asked to continue only with topics considered critical. This topic was judged to be of critical importance so the process of the appraisal continued. NICE was aware that NHSE had considered the exceptional circumstances and issued time-limited guidelines to make oral treatments (enzalutamide or abiraterone) available in place of docetaxel. No changes were made to NICE processes or methods as a result of the pandemic. She observed that making changes to NICE methods for a time-limited event would have major implications for the programme.

59. Professor James, for BUG, questioned the idea that COVID-19 is necessarily time limited and emphasised that the seriousness of the pandemic was very clear by the time the FAD was published in June 2020.

60. Helen Knight, for NICE, acknowledged that if COVID-19 does indeed remain a long term problem then this may need to be considered in future. However, the NHSE interim policy will apply until April 2021, so this takes account of the additional benefits of abiraterone during the pandemic until that time.

61. The Appeal Panel noted that the final Committee meeting was held in January 2020, before the pandemic was declared, so the Committee could not have taken account of this during the appraisal. Once the impact of the pandemic became clear, BUG

highlighted the potential additional benefits of abiraterone over docetaxel to NHSE (rather than NICE), who acted quickly to make the treatment available during this period. NICE followed the advice they were given to prioritise critical topics but not to make any changes to their methods. The Panel could not see any unfairness in the approach that has been taken. The significance of COVID-19 for NICE appraisals in future is not a matter for the Appeal Panel.

62. The Appeal Panel therefore dismissed the appeal on this point.

### ***Appeal by Janssen***

#### **Appeal Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly.**

**Janssen Appeal Ground 1a.1a:** The Appraisal Committee has failed to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured: (a) capture of benefits in the QALY for abiraterone.

63. Dr Williams, for Janssen, stated that NICE methods require Committees to take account of whether Quality of Life (QoL) benefits have been adequately captured in the modelling whenever ICERs are over £20,000. She argued that QoL benefits had not been adequately captured in this case. She said that the Committee had not given reasons for their judgment on this issue and therefore the process was not sufficiently transparent.
64. Ross Dent, for NICE, stated that both the reduced QoL associated with docetaxel and the increased QoL associated with abiraterone (versus ADT alone) had been captured in the model. He said that the company had not raised any concerns about the utility values used in the modelling.
65. Fiona Davies, for Janssen, said that the EQ5D might not capture all aspects of QoL such as improvements in pain and fatigue, or reduced anxiety about chemotherapy. She also argued that the small decrement in utility modelled for docetaxel was not consistent with the fact that two thirds of patients did not receive this treatment.
66. Ross Dent, for NICE, referred to section 5.3 of the methods guide, explaining that there are specific steps required to show that the EQ5D is not a suitable tool. These were not present in this appraisal.
67. Dr Williams, for Janssen, responded by saying that the company accepted the use of the EQ5D in the modelling, but nevertheless the Committee were required to consider whether this had captured all the benefits of treatment.
68. Dr Latimer, for the appraisal committee, said that this consideration is of particular relevance when ICERs are close to the threshold normally considered cost-effective, or when there is uncertainty about this. In this case, there was a very high degree of certainty that the ICER was considerably above the threshold and so a small uncaptured QoL benefit would not have affected the Committee's decision.

69. The Appeal Panel noted that section 6.3.3 of the methods guide states, “Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors ... Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured”. The Panel did not understand this to amount to a requirement for Committees to discuss this issue explicitly in every FAD. The Panel’s interpretation of paragraphs 6.3.4 and 6.3.5 of the methods guide was that considerations should be explicit when the ICER is in the range £20,000-£30,000. In this case, the FAD stated that the ICER was “considerably higher than the range normally considered a cost-effective use of NHS resources”. The Panel judged that it was implicit in this statement (and clear to an informed reader) that this meant the ICER was higher than £30,000.
70. The Panel were not persuaded that there were strong reasons to suggest that change in QoL had been inadequately captured in this appraisal. Taken together with the fact that the ICER was considerably higher than the range normally considered cost-effective, the Panel judged that the absence of explicit discussion of this issue in the FAD did not amount to unfairness.
71. The Appeal Panel therefore dismissed the appeal on this point.

**Janssen Appeal Ground 1a.1b:** The Appraisal Committee has failed to consider whether and, if so, to what extent the change in health-related quality of life associated with use of abiraterone has been adequately captured: (b) Aspects of the technology that relate to non-health objectives of the NHS.

72. Dr Williams, for Janssen, referred to paragraph 6.3.3 of the methods guide which asks Committees to take account of specific factors when the most plausible ICER is >£20,000. In particular, this section refers to, “Aspects that relate to non-health objectives of the NHS”. She argued that this would include the need for the NHS to improve efficiency or the impact of a treatment on NHS capacity. She stated that the FAD provides no evidence that this factor had been considered by the Committee, and that this was unfair.
73. Fiona Davies, for Janssen, highlighted the fact that abiraterone is an oral treatment and helps to keep patients out of hospital. This frees up space in chemotherapy units, allowing other patients to be treated. She argued that these factors are always important, but their importance has been amplified by the current COVID-19 pandemic.
74. Professor Adler, for the appraisal committee, explained that the Committee was satisfied that the costs and utilities associated with these factors were accounted for in the model.
75. Helen Knight, for NICE, pointed out that paragraph 6.3.3 of the methods guide refers on to paragraphs 6.2.20 and 6.2.21 on this specific issue. These sections go on to say that costs and benefits outside the NHS can be considered only when this is

requested by the Department of Health and Social Care as part of the remit of the appraisal.

76. Dr Williams, for Janssen, disagreed with this interpretation of the methods guide. She agreed that such costs and benefits could only be included in the modelling when this was requested by the Department of Health and Social Care but argued that these factors should be given consideration in all cases.
77. Professor Adler, for the appraisal committee, said that she did not accept Janssen's argument that benefits for NHS capacity were distinct from the costs of hospital visits and appointments captured in the model. Dr Latimer, for the appraisal Committee, said that the "Non-health benefits" referred to in Janssen's appeal letter (the value of an oral treatment, and the value of a treatment that does not cause immunosuppression) were modelled.
78. As set out in the discussion of Appeal Point BUG 1a4, the Panel did not accept that there was any unfairness with regard to the impact of COVID-19 on the appraisal.
79. The Appeal Panel also specifically considered Janssen's argument about the non-health benefits of abiraterone. The Panel was uncertain about whether effects on NHS capacity should be considered a "non-health" benefit, but recognised their importance. It accepted the Committee's position that many aspects of the impact of the treatment on NHS capacity were indeed modelled, but also accepted that there could be aspects which were not fully captured in the modelling. The Panel did not understand paragraph 6.3.3 of the methods guide to amount to a requirement for committees to discuss this issue explicitly in every FAD. The Panel's interpretation of paragraphs 6.3.4 and 6.3.5 of the methods guide was that these considerations should be explicit when the ICER is in the range £20,000-£30,000. In this case, the FAD stated that the ICER was "considerably higher than the range normally considered a cost-effective use of NHS resources". The Panel judged that it was implicit in this statement (and clear to an informed reader) that this meant the ICER was higher than £30,000. Therefore, the Panel judged that the absence of explicit discussion of this issue in the FAD did not amount to unfairness.
80. The Appeal Panel therefore dismissed the appeal on this point.

**Janssen Appeal Ground 1a.2c:** The Appraisal Committee's conclusion that "*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination*" does not: (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223.

81. Dr Williams, for Janssen, highlighted the substantial unmet need among patients who cannot or should not be treated with docetaxel. She said that the statement in the FAD that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" conflicts with the position of NHSE (in its commissioning policy for docetaxel) and the position taken by NICE in other appraisals (specifically the appraisal of Radium-223). She emphasised the requirement for transparency as part of a fair process, and said that the reasons for

taking a different approach from NHSE and previous appraisals should have been made explicit in the FAD.

82. Professor Adler, for the appraisal committee, said that the Committee were aware of the NHSE commissioning policy for docetaxel (referred to in the FAD at paragraph 3.2) but also noted clinical expert opinion that fitness for docetaxel is not necessarily clear cut or easy to operationalise. She quoted Professor James' comment at the hearing, describing this definition as "slippery" and his previous comment in an email about a "larger number who are chemo-borderline".
83. Professor Adler also noted that the Committee were not presented with evidence on the use of abiraterone in men who were not fit for chemotherapy. She responded to the point regarding consistency with the appraisal of Radium-223, saying that in that appraisal the Committee were specifically given evidence of the efficacy of the therapy in patients who could not take docetaxel.
84. Dr Williams, for Janssen, said that the inconsistency with the Radium appraisal is that in the Radium-223 appraisal it was accepted that clinical consensus could be used to define the group of patients who could not have docetaxel. She argued that no reasons for departing from that approach were given in the FAD (or at the hearing).
85. Ross Dent, for NICE, said that the Committee had considered cost-effectiveness in patients who could not have docetaxel by looking at the cost-effectiveness of abiraterone against ADT alone. The conclusion was that abiraterone is not cost-effective for this group.
86. There is further discussion on the reasonableness of the conclusion that it was not possible to define a sub-group of patients who could not receive docetaxel under Janssen 2.2 and PCUK/TPC 2.1 (paragraphs 193-204 and 144-154 of this letter). This particular appeal point concerns the fairness of the decision with regard to the reasoning for the different approach taken compared with the Radium-223 appraisal.
87. As previous Appeal Panels have noted, whilst appraisal committees should seek to ensure, as far as possible, that their judgements are applied consistently between appraisals, this expectation must not be set too high. The circumstances of every appraisal are different, and past approaches may be departed from with appropriate reasoning. In this case, the two appraisals concerned the same disease, and both attempted to define a group of patients who could not receive docetaxel. In the Radium-223 appraisal the Committee decided that a clinical consensus approach could be used to operationalise this definition, whereas in this appraisal the Committee concluded from expert evidence that this was not possible. The approach used in the Radium-223 appraisal was raised by PCUK/TPC in their response to the ACD. The Committee's response to this at consultation was to refer to paragraph 3.2 of the FAD. The Panel judged that this section of the FAD did not adequately explain the reasons why the approach used in the Radium appraisal was not considered suitable here. At the hearing, the Panel heard that the Committee were concerned that no evidence had been presented on the use of abiraterone in men who were not fit for docetaxel (in contrast to the Radium appraisal). However, the Panel judged



that this was a different issue from the question of whether the subgroup of patients unfit for docetaxel could be defined. The Panel therefore concluded that the reasons for departing from the approach taken in a previous closely-related appraisal had not been made sufficiently transparent and this constituted procedural unfairness.

88. The Appeal Panel therefore upheld the appeal on this point.

89. The Institute should now explicitly consider the question of whether the approach used in the radium appraisal to define a sub-group of patients ineligible for docetaxel could also be used in this appraisal. If it concludes that it cannot use this approach, the reasons for this should be clearly stated.

**Janssen Appeal Ground 1a.3:** The Appraisal Committee has provided no reasons to explain its view that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel

90. Dr Williams, for Janssen, stated that there was no reason to suppose that the benefits of treatment with abiraterone would differ between the populations who could or could not receive docetaxel. The marketing authorisation for abiraterone covered both populations. It was unacceptable to say that the benefits of treatment may be different without explanation; how were consultees supposed to respond? There might be many reasons not to receive docetaxel, and abiraterone had a different mechanism of action. Further the lack of reasoning was inconsistent with proper decision making.

91. Mohamed Lockhat, for Janssen, added there was no biological reason why the results of treatment would differ between the populations.

92. Professor James, for BUG, said that the distinction between people who could and could not receive docetaxel was rather arbitrary. For example some people might not receive chemotherapy early in their disease, but would receive it later if their fitness changed. But there was a population that was relatively more chemotherapy-unfit. He confirmed there was no reason to think abiraterone worked differently in these two populations, and also that chemotherapy-ineligible patients did respond to treatment with abiraterone. When recruitment to the docetaxel arm of STAMPEDE closed in 2013, the recruitment rate went up. The age profile of patients enrolled increased by two years. The trial population was being enriched with more people who would not have received docetaxel. But the hazard ratio improved. And there was no suggestion that adding more docetaxel ineligible patients had had an effect on efficacy.

93. Professor Adler, for the appraisal committee, explained that in TA 232 the appeal panel had advised that Committees must look at the whole licensed population, and only having done so could they look for subgroups. Committees must not begin by looking at subgroups.

94. Dr Latimer, for the appraisal committee, added that the Committee was not presented with evidence that was specific to the population who did not receive docetaxel. It had no modelling that excluded docetaxel. STAMPEDE could not be

regarded as consisting of docetaxel eligible and ineligible populations, and in any event the post 2013 subgroup was not presented to the Committee. If you looked at other proxies for chemotherapy eligibility, e.g. ECOG score, you might reach a different conclusion on the effect of abiraterone in the population who do not receive docetaxel. Further the Committee did look at an ICER comparing abiraterone to ADT only, using data on clinical effectiveness from the whole population (i.e. assuming equal efficacy) and this generated a very high ICER. The FAD at paragraph 3.2 does not state that the Committee thought the benefits would differ, it stated that the Committee did not have data and did not know the clinical efficacy in this population. But even so it had generated an abiraterone vs ADT ICER and found it to be too high.

95. In response to a question from Professor James, Helen Knight explained that, following its guidance, NICE had used the current list price for abiraterone in its calculations. Professor James considered that to be unreasonable. Ms Knight added that the company had provided a discounted price but this had not been approved by NHSE. With no agreement on price it was not modelled.
96. Nicola Trevor, for Janssen, clarified that so far as the company was concerned NICE could have modelled the treatment at the discount it had offered.
97. Professor Adler repeated that the Committee had not asserted that treatment effects were different in the two populations; it said that it did not know they were the same. She added the population who did not have docetaxel were more likely to have comorbidities and these could be effect modifiers. The Committee had asked the company for the direct analysis from STAMPEDE, and it had run a comparison with ADT anyway which assumed equal clinical benefit.
98. In response to a comment from Dr Latimer that the chemo-ineligible population would have an ECOG of 3 or worse, and that Peter Clarke of the Cancer Drugs Fund had told the Committee that all the trial populations were fitter than the “all comers” NHS patient population, Professor James replied that he would not prescribe abiraterone for patients with an ECOG of 3 or 4 either, and that chemotherapy-unfitness was more multifactorial.
99. Responding to a question whether NICE would only obtain relevant information from the manufacturer, Helen Knight said that NICE would consider seeking further information but it had to act within its processes. The challenge was this was a long appraisal and the Committee were constantly looking at new evidence: they did rely on stakeholders to alert them to new information. There had to be a cut-off for new information, and this appraisal had become protracted for commercial reasons. Dr Latimer added that the Committee had considered a new company submission in 2020, and the ERG had considered a 2018 published paper using STAMPEDE quality of life data. He repeated there was no chemotherapy-unfit subgroup presented.
100. Karen Stalbow, for PCUK, challenged that if the Committee knew abiraterone had benefits for all and it knew there was a population who would only receive ADT, why was it necessary to be so specific about benefit in a chemo-unfit population?

Professor Adler replied the Committee could simply have written a highly-abbreviated FAD stating that the ICERs were far too high. (She noted that the Scottish Medicine Consortium had published an ICER of around £200,000 for abiraterone using the list price.) The reason that they did not do that, but rather considered every aspect of the evidence, was that the Committee want to help to eventually reach a positive decision.

101. The Appeal Panel concluded as follows - while the FAD could and perhaps should have been clearer, the Panel was satisfied that the Committee had not been asserting that there were different effects of treatment in patients unable to receive docetaxel. There could be no obligation to give reasons for a statement that was not made. Insofar as the Committee were by implication saying that it could not be assumed without some evidence that the benefits would be the same, the Panel felt that while it would have been more transparent to explain the thinking behind that position, the reasons would or should be apparent to anyone engaging with the appraisal. The Panel therefore concluded there had been no unfairness. The proposition that, in order for a subgroup to be considered the Committee must be presented with evidence of benefit in that subgroup, did not need explanation.

102. The Panel also noted that the Committee had calculated an ICER for the ADT population, using an assumption of equal clinical effectiveness, and had concluded that the ICER was too high to make a positive recommendation. The Panel did not lose sight of the fact that this appeal point was brought as a matter of fairness. The Panel reminded itself that if an unfairness had been found then the Panel should only conclude that the unfairness made no difference to the outcome if it were certain that that must be the case. This was a case where it could have been certain. The Committee had actually performed an analysis using the very assumption that the appellants argued it had rejected without reason and the ICER nevertheless exceeded the range normally accepted as cost-effective.

103. The Panel has found that the Committee did not assume that there were different effects of treatment in patients unable to receive docetaxel, and that although the FAD could have been clearer, any lack of clarity did not amount to unfairness. The Panel is also clear the Committee's uncertainty about whether treatment effects were equal in the docetaxel-ineligible population had definitely made no difference to the guidance, because the ICER calculated on the equal-benefit assumption was too high.

104. The Appeal Panel therefore dismissed the appeal on this point.

**Janssen Appeal Ground 1a.4:** The conclusions of the Appraisal Committee in relation to the cost-effectiveness of abiraterone in this appraisal are opaque.

(At initial scrutiny this appeal point had been been agreed as valid insofar as it relates to the failure to provide an ICER range.)

105. Dr Williams for Janssen, stated that the Committee's conclusions on the ICERs in this appraisal were unclear. This mattered for two reasons: transparency promoted effective engagement with the appraisal, and it allowed quality assurance

of the decision. The Committee should be held to high standards but no detail was given, merely that the ICERs were “considerably higher” or “higher” [than the usual range considered cost-effective]. Dr Williams understood why exact ICERs could not be given but a range of ICERs could be given, as NICE’s methods required. Without that information, parties did not know what they had to do to secure a positive outcome. The company itself had calculated that the ICER would be cost-effective, as had the STAMPEDE trial team.

106. There was an unfair circularity, with NICE arguing that it would only consider a price approved by NHSE, and NHSE saying it would only agree a discounted price that gave an outcome that NICE considered cost-effective, but the company being unable to work out what that would be. She observed that NHSE had the information that the company did not have and NICE were practically sitting at the table with them.
107. Professor Adler, for the appraisal committee, and Helen Knight, for NICE, agreed that transparency was important. NICE does accept confidential information (in this case the price of comparator drugs) and it cannot be released without consent. The Committee had stated that the ICERs were above the usual range and it was general knowledge that that meant above £30,000. This was in line with what had been discussed with the Association of the British Pharmaceutical Industry (ABPI). The company had the same models as the Committee and it had the Committee’s preferred assumptions so it could run its own modelling.
108. Dr Williams replied that the company was concerned with the modelling of its product both at list price and at offer price. The appeal was the first time the company had been told the ICER was above £30,000. The company needed to be given the Committee’s preferred ICER range, the ERG report was not enough because the ERG was not the Committee.
109. Ross Dent, for NICE, accepted that the Committee could have been clearer in publishing an ICER range. It could have made clear the ICERs were above £30,000. Professor Adler agreed the Committee could have been more granular, though possibly not giving more detail than that the ICERs were over £30,000. Helen Knight added that the Committee could have given ICERs using all products’ list prices.
110. Nicola Trevor, for Janssen, added that the ICER range would have made a difference to the company. She said that their model gave an ICER of under £20,000, the STAMPEDE team also thought the treatment was cost-effective, and yet the FAD says that treatment was not cost-effective even at the discounted price.
111. Dr Williams said that an indication that the ICER was above £30,000 would not be enough. Returning to the point on day two of the appeal she said enquiries had been made of the ABPI and they did not agree that their position was that NICE could only indicate if an ICER was below £20,000, between £20,000 and 30,000, or above £30,000. The ABPI said that ICER ranges of £10,000 increments had been discussed.

112. Helen Knight, for NICE, added that while £10,000 ranges were being considered this was not yet in place. NICE acknowledge that they should have provided an ICER range using the list price of all products but could not have published an ICER range using confidential prices in comparator patient access schemes.
113. The Appeal Panel concluded as follows. It is of the highest importance that NICE can receive information in confidence and can honour that confidentiality. Without this ability it will not be able to perform its tasks. Further, the actual price of a competitor product must be at the highest end of any hierarchy of information required to be kept confidential.
114. Against this, the Committee's preferred ICER or range of ICERs is a very important part of understanding its conclusions in an appraisal. The Panel agrees publication of ICER(s) will normally be very desirable both to enable comment during an appraisal and to quality assure guidance when an appraisal is complete.
115. This tension between confidentiality and transparency is not a new issue. NICE is aware that confidentiality may prevail, but only if it has taken all reasonable steps to be as transparent as possible. This position was upheld in the *Servier* litigation.
116. The Panel understands that publication of an exact ICER would enable anyone with access to the economic model to deduce the actual price of competitor products. Clearly therefore that is not possible, and to that extent transparency must give way to confidentiality. What the Committee did not explain was why it was not possible to have given any more information about the calculated ICERs and still not have revealed the price of competitor products.
117. The Appeal Panel therefore upheld the appeal on this point.
118. The Institute must now consider whether it is possible to give any more precise indication of the ICERs calculated, while not compromising the confidentiality of competitor pricing. For example, a range might be given, within which the actual ICER falls. How broad or narrow the range would have to be to preserve confidentiality would depend on the model, and the Panel cannot take a view.
119. If this is not possible then the Panel would expect the Institute to be able to justify that conclusion.
120. If it is possible to give a range of ICERs then the Institute must ensure that participants in the appraisal are given a chance to make observations on the ICERs and anything driving the ICERs, and that the Committee can consider those observations and whether the guidance should be revised as a result. One way to achieve this could be a further round of consultation.

**Janssen Appeal Ground 1a.6:** The Committee's statement that *"the clinical experts involved in STAMPEDE confirmed that post-progression survival was shorter after*

*abiraterone in combination than after ADT in this trial*” is based on unpublished data that have not been disclosed or confirmed.

121. Dr Williams, for Janssen, stated that this statement was based on oral testimony from the clinical expert in May 2018. It was a controversial statement. Two years have now passed. No data have been published to back up the statement. Janssen told the Committee they considered the statement to be wrong. It was also unbalanced in not referring to benefit pre-progression.
122. Professor Adler, for the appraisal committee, said she felt it was reasonable to accept the expert’s evidence. Dr Latimer, also for the appraisal committee, added that the relevant paragraph of the FAD (3.7) related to a comparison of docetaxel and abiraterone and described STAMPEDE and the company meta-analysis. Abiraterone showed a good relative effect on progression free survival but the results were equivocal on overall survival. The only logical explanation was that post progression survival was longer with docetaxel. FAD paragraph 3.7 had to be read *in toto* as a full discussion of the evidence: there was not reliance on a “single unsupported statement”.
123. Dr Williams replied that the statement was old and probably no longer correct. She argued that it was incumbent on the Committee to explore whether this statement remains correct two years later.
124. Dr Latimer said the question was “what was the real benefit to overall survival?” and the expert comment was more of an interpretation point.
125. Professor James, for BUG, said that abiraterone showed a strong benefit over docetaxel for progression free survival, but the relative impact on overall survival was unclear. Therefore post progression survival must be better for docetaxel, though by how much was unknown. He was about to publish these data.
126. The Appeal Panel concluded as follows - the statement referred to was part of the overall evidential picture considered by the Committee, and was more by way of a comment on the data than data in itself. The Panel did not think there was anything unfair in the fact that the data on post progression survival had not yet been published and the Committee were entitled to draw on an expert view as part of their overall evidence base. The view had been given some time ago but the clinical expert had repeated his view at the appeal hearing, and in any event it appeared to be a logical consequence of the published trial data. The Panel did not think there was any obligation on the Committee to have sought to “refresh” the view in this case, nor that there was anything unfair in the opinion being based on data that were currently unpublished. Janssen knew what the opinion was and had had a chance to challenge it which is what fairness required.
127. The Appeal Panel therefore dismissed the appeal on this point.

**Janssen Appeal Ground 1a.7:** The Appraisal Committee’s focus on number of subsequent treatment options rather than outcomes relies on an irrelevant consideration.

128. Nicola Trevor, for Janssen, stated that the focus on treatment options rather than outcomes was an irrelevance. The effect on progression free survival, overall survival and quality of life were all that mattered. Abiraterone had demonstrated significant benefits at this point in the treatment pathway and so the focus on the number of subsequent treatments was unfair.
129. Professor Adler, for the appraisal committee, replied that if trial participants received life extending treatments in different ratios to NHS patients then that had to be considered. Dr Nick Latimer, for the appraisal committee, added that you cannot ignore subsequent treatments. The methods guide made clear that what has to be compared is different treatment sequences. NICE takes a lifetime horizon as is well known. Subsequent treatments affect subsequent costs and benefits and are clearly relevant to modelling lifetime benefits. The Committee had not looked at subsequent treatments instead of primary outcomes, but in addition to them.
130. Nicola Trevor replied that she was not suggesting subsequent therapies should be ignored, but the focus on the number of treatments rather than overall survival was an error. Professor Adler had stressed that using abiraterone early in the treatment pathway reduced later options which Janssen thought was irrelevant.
131. Professor James, for BUG, added that for each patient you would have a global discussion about treatment pathways. For each subsequent treatment there was less benefit. The number of treatment lines had little impact on overall survival. Later lines would be short and of little benefit or cost. It was how many treatments a patient can receive that work that matters. You would try as many active treatments as you could.
132. Dr Latimer, for the appraisal committee, said that paragraph 3.7 of the FAD began by giving the hazard ratios from all the data sources, and then discussed why those hazard ratios might vary. But it is the clinical trial results that are fed into the models. The company submitted various configurations of post study treatments, but all the overall survival estimates used in the model were from LATITUDE. The company base case modelled that 80% of patients who had received docetaxel would go on to abiraterone or enzalutamide, but took its survival data from LATITUDE: so that gave a mismatch adding cost to the comparator arm because in LATITUDE only 50% of patients had further active treatment. He felt the Committee had done exactly what the company were saying it should have done.
133. The Appeal Panel concluded as follows - it was satisfied that the Committee had correctly modelled the impact of treatments on overall survival, progression free survival and quality of life, and had not inappropriately focused on the number of subsequent lines of treatment as a consideration in itself.
134. The Appeal Panel therefore dismissed the appeal on this point.

### ***Appeal by Prostate Cancer UK and Tackle Prostate Cancer (PCUK/TPC)***

**Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.**

135. There was no appeal under this ground.

### ***Appeal by the British Uro-Oncology Group (BUG)***

**Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.**

136. There was no appeal under this ground.

### ***Appeal by Janssen***

**Appeal Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers.**

**Janssen Appeal point Ground 1b.8** The assertion by the Appraisal Committee that it is required to say whether abiraterone is “safe” in patients who cannot take docetaxel assumes the role of the regulatory authority.

137. Dr Williams, for Janssen, explained that the European Medicines Agency (EMA), when considering whether to grant a marketing authorisation, must look at a product’s safety, quality, and efficacy. By granting a marketing authorisation to abiraterone the EMA had determined that it was acceptably safe, and the balance of risk and benefit of treatment with abiraterone was positive.

138. In contrast NICE must issue guidance on clinical and cost-effectiveness. When assessing clinical effectiveness NICE may consider the impact of adverse events. However it may not consider if a product is “safe”. That is not its role. Also it lacks the data to do so reliably, for example it has no access to pharmacovigilance data.

139. Professor Adler, for the appraisal committee, felt the point was being taken out of context. The relevant paragraph of the FAD (3.2) had to be read in full. The Institute’s methods guide was clear that adverse events had to be taken into account and the Committee had applied a disutility to reflect adverse events. She accepted that the wording was “not the best”.

140. Dr Williams said that the FAD referred to safety but the Committee should have assessed if adverse events affected clinical effectiveness.

141. The Appeal Panel concluded as follows - it agreed that an assessment of safety per se was for the regulator and not for NICE. It also agreed that adverse events could have an impact on clinical and cost-effectiveness and so were relevant to NICE’s decision making. It was satisfied that the Committee had properly considered adverse events only in the context of their impact on clinical and cost-effectiveness, and had not assumed the role of the regulator.



142. Therefore the Panel dismissed the appeal on this ground.

143. However the Institute should consider whether the relevant wording of the FAD could be improved, to make clear that the point being made is around uncertainty of the impact of adverse events on clinical and cost-effectiveness.

### ***Appeal by Prostate Cancer UK and Tackle Prostate Cancer (PCUK/TPC)***

#### **Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.**

**PCUK/TPC Appeal point Ground 2.1:** The recommendation is unreasonable in the light of the evidence submitted to NICE concerning the effectiveness of abiraterone in patients who cannot receive docetaxel.

144. Heather Blake, for PCUK, stated that when the Committee were struggling to define the populations who cannot take docetaxel, they should have consulted clinical experts for guidance and sought additional sources of information. The Committee should also have provided clear reasons for not following the approach taken in the Radium-223 appraisal. Finally, she stated that it was unreasonable for the Committee not to use ADT alone as their preferred comparator.

145. Professor James, for BUG, said that the increase in recruitment rate to the STAMPEDE trial when the docetaxel arm closed demonstrates that clinicians can identify patients who cannot have docetaxel but are suitable for abiraterone.

146. Karen Stalbow, for PCUK, said that the average age and frailty score of patients recruited to STAMPEDE went up once the docetaxel arm closed, showing that patients unfit for chemotherapy were then recruited to the trial.

147. Professor Adler, for the appraisal committee, noted clinical expert opinion that fitness for docetaxel is not necessarily clear cut or easy to operationalise. She quoted Professor James' comment at the hearing, describing this definition as "slippery" and his previous comment in an email about a "larger number who are chemo-borderline".

148. Dr Patel, for the appraisal committee, said the Committee were aware of the need to operationalise any definition in a way that could be applied consistently in clinical practice and they had heard from clinical experts that this was difficult.

149. Dr Latimer, for the appraisal committee, said the appraisal committee were not presented with any evidence of the efficacy of abiraterone in those unfit for chemotherapy. If chemotherapy-unfit patients were included in the STAMPEDE and LATITUDE trials, the Committee were never presented with an analysis on these patients. In addition, the Committee was never presented with a cost-effectiveness analysis that excluded docetaxel from the treatment pathway. The company provided a model said to relate to chemotherapy-ineligible patients, but this modelled a large proportion of patients in both groups receiving docetaxel after relapse.

150. Dr Latimer, for the appraisal committee, stated that the Committee did consider ICERs for abiraterone versus ADT alone. These ICERs were still much higher than the range usually considered a cost-effective use of NHS resources. He said that the Committee did not ignore the chemotherapy-unfit group, but just were not provided with any evidence or analyses for that group.

151. The Appeal Panel were aware of the Tameside duty, which requires a Committee to take reasonable steps to obtain the necessary evidence before reaching a conclusion. In this regard, the Panel noted that the Committee were aware of various approaches to defining a docetaxel ineligible subgroup (including the Radium-223 appraisal and the NHSE commissioning policy) and had sought expert advice. The Panel was satisfied that reasonable steps were taken to obtain relevant evidence. The Panel was also satisfied that the Committee had considered ADT alone as a comparator, and that it was reasonable to also consider docetaxel as a comparator.

152. However, the Panel were concerned that the reasoning for the Committee's conclusion that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" was not clear. Given that clinical criteria to define eligibility for docetaxel do exist, the Panel judged that a reasonable Committee should give clear reasons why these criteria were not suitable in the current appraisal. The approach used in the Radium-223 appraisal was raised by PCUK/TPC in their response to the ACD. The Committee's response to this at consultation was simply to refer to paragraph 3.2 of the FAD. As discussed under appeal point Janssen 1a2c, the Panel judged that this section of the FAD did not adequately explain the reasons why the approach used in the Radium appraisal was not considered suitable here. At the hearing, the Panel heard that the Committee were concerned that no evidence had been presented on the use of abiraterone in men who were not fit for docetaxel (in contrast to the Radium appraisal). However, the Panel judged that this was a different issue from the question of whether the subgroup of patients unfit for docetaxel could be defined.

153. The Appeal Panel therefore upheld the appeal on this point.

154. The Institute should explicitly consider whether it is possible to define a group of patients who are ineligible and/or unsuitable for docetaxel, before going on to consider whether there is evidence available for the effectiveness and cost-effectiveness of abiraterone in that group. If it concludes that approaches taken in other settings are not suitable in this appraisal, it should give clear reasons for this.

### ***Appeal by the British Uro-Oncology Group (BUG)***

**Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.**

**BUG Appeal point Ground 2.1:** Point 1 The statement *"There are concerns that the trials may overestimate the effectiveness of abiraterone. This is because the treatments offered in the trials after the disease progresses do not reflect those offered in the NHS, where more*

*people on standard care have effective treatments after their disease progresses than in the trials.*" is unreasonable.

155. Professor James, for BUG, stated that the idea that the salvage therapies used in the STAMPEDE trial were sub-optimal is not plausible. He said that participation in clinical trials is often a marker of the quality of trusts and clinicians, and that 110 oncology centres took part in the study. He said that the full range of relevant salvage therapies were available during the time STAMPEDE was recruiting, and so it is simply implausible that this study did not reflect standard NHS practice. He added that survival in the control arm of STAMPEDE is almost identical to that seen in many other clinical trials.

156. Dr Latimer, for the appraisal committee, said that the Committee had expected STAMPEDE to reflect NHS clinical practice. However, the FAD sets out at paragraph 3.8 how it actually seemed to differ. Firstly, a small proportion of patients received abiraterone or enzalutamide after previous abiraterone treatment. Secondly, only 55% of patients initially treated with ADT alone had follow-on treatment with abiraterone. This is substantially lower than the 80% estimated by the company (based on clinical opinion and UK market share) to reflect current NHS clinical practice. The Committee suspect that the reason for this discrepancy is that abiraterone for relapsed disease was not available during the earlier part of the trial. He explained that despite the Committee's concerns that the trials may not capture all the benefit of follow-on treatments in current NHS practice, they nevertheless used this data in the appraisal.

157. The Appeal Panel noted the substantial difference in the use of follow-on abiraterone between the STAMPEDE trial and the company's estimate of current practice, and were persuaded that there was a plausible reason for this. They were satisfied that the Committee had given clear reasons for the statement referred to in the appeal point, both in the FAD and during the hearing. They were not persuaded that this was an unreasonable conclusion to draw from the evidence.

158. The Appeal Panel therefore dismissed the appeal on this point.

159. However the Institute should consider whether the relevant wording of the FAD could be improved, to make clear there is a plausible reason for the apparent discrepancy (i.e. that abiraterone for relapsed disease was not available during the earlier part of the STAMPEDE trial).

**BUG Appeal point Ground 2.2:** Point 3 The statement *"It is not appropriate to consider separately the clinical and cost-effectiveness of abiraterone in combination in people who currently have ADT alone"* is unreasonable.

160. Professor James, for BUG, stated that there is no reason to think that abiraterone works less well in a chemotherapy-unfit population. He explained that when the docetaxel arm of STAMPEDE closed, the patients randomised were older and had worse performance status, suggesting that chemotherapy-unfit men were now being randomised. The hazard ratio for benefit actually improved after this time.

161. Dr Latimer, for the appraisal committee, acknowledged that some chemotherapy-unfit patients were probably recruited after the docetaxel arm of the trial closed in 2013. However, comparing hazard ratios before and after 2013 is not a chemotherapy fit v unfit comparison. The Committee were not presented with any evidence on the effectiveness of abiraterone specifically in patients unable to take docetaxel. In addition, the Committee were never presented with a cost-effectiveness analysis that excluded docetaxel from the treatment pathway. (The company provided a model said to relate to chemotherapy-ineligible patients, but this modelled a large proportion of patients in both groups receiving docetaxel after relapse.) He also said that there is some trial data to suggest that abiraterone may be less effective in older patients or those with higher ECOG scores (greater frailty). Despite this, the Committee did consider ICERs for abiraterone versus ADT alone (a proxy for the chemotherapy-ineligible group) and this modelling assumed that abiraterone is equally effective in this group.

162. The Appeal Panel concluded as follows – in related appeal points, the Panel has found that the Committee’s position that it could not define a group of patients ineligible for docetaxel was unfair (in relation to failure to provide reasons for not following the approach used in the Radium appraisal, Janssen 1a2c) and unreasonable (Janssen 2.1 and PCUK 2.1) (see paragraphs 81-89, 180-192 and 144-154 above). However, the question of whether this subgroup could be defined is distinct from the question of whether evidence was available for this subgroup. The Panel judged that it was reasonable to conclude that there was insufficient evidence to consider separately the clinical and cost-effectiveness of abiraterone in this group. The Panel also agreed that it was reasonable that the Panel had considered the cost-effectiveness of abiraterone versus ADT alone (as a proxy for this group).

163. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal point Ground 2.3:** Point 4 The statement “*The clinical experts explained that people who have previously had docetaxel as first-line treatment in the hormone-sensitive setting can have docetaxel again (for up to an additional 10 cycles)*” is unreasonable.

164. Professor James, for BUG, acknowledged that patients can be re-treated with docetaxel (but not abiraterone) on relapse, but questioned the quantitative impact of that. Recent data suggests that the impact of docetaxel re-challenge is less than when it is used first line. Whilst it is theoretically possible for patients to have an additional 6-10 cycles of docetaxel, in practice most would not tolerate this due to cumulative toxicity.

165. Professor James said that because around 80% of patients are not able to have re-treatment with docetaxel it is unreasonable for this to form part of the rationale for not recommending abiraterone.

166. Dr Patel, for the appraisal committee, stated that it was factually correct to say that people can have re-treatment with docetaxel. He emphasised that this statement was made in the clinical management section of the FAD, which aims to show the place of the technology being appraised alongside other treatment options.

167. The Appeal Panel noted that there was agreement that it was correct to state that patients can have re-treatment with docetaxel, so it was not unreasonable to make this statement in the FAD or to consider this in the appraisal. The Panel was not persuaded that this had played a role in the Committee's decision that could be considered to make the decision unreasonable.

168. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal point Ground 2.4:** Point 5 The statement "*The comparison of abiraterone and docetaxel suggest that there may be no difference in overall survival*" is unreasonable.

169. Professor James, for BUG, explained that there are two ways to compare outcomes with abiraterone and docetaxel. One is to use direct randomised evidence. With this method, abiraterone is superior for progression free survival, but overall survival looks similar. The second method is to use a network meta-analysis. This method also shows that abiraterone is superior for progression free survival, but also gives a 94% probability that abiraterone is superior for overall survival.

170. Professor Adler, for the appraisal committee, highlighted the hazard ratio of 1.13 in STAMPEDE, suggesting that abiraterone could be inferior in terms of overall survival. She said that Health Improvement Scotland had also concluded that there was uncertainty about whether abiraterone improves overall survival.

171. Dr Latimer, for the appraisal committee, stated that section 3.7 of the FAD discusses both the direct RCT evidence and the network meta-analysis. For overall survival, the STAMPEDE data favours docetaxel (with the confidence intervals crossing 1) and the meta-analysis favours abiraterone (with the confidence intervals crossing 1). Any statistician would therefore conclude that it is uncertain whether abiraterone increases overall survival. The Committee considered ICERs for scenarios where overall survival is equal for docetaxel and abiraterone, but also considered scenarios using the hazard ratio from the network meta-analysis. Under all these scenarios, the ICERs were higher than those usually considered cost-effective.

172. The Appeal Panel agreed that the appraisal committee had considered all relevant evidence. The Panel judged that it was reasonable to conclude that there may be no difference in overall survival between abiraterone and docetaxel.

173. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal point Ground 2.5:** Point 6 The statement "*The magnitude of OS benefit for abiraterone may be over-estimated*" (section 3.6) is unreasonable.

174. In their appeal letter, BUG say that this does not seem a supportable statement because two RCTs of abiraterone produce near identical results. Furthermore, the magnitude of benefit with abiraterone is strikingly similar to that of enzalutamide, so this seems to be a consistent class effect.

175. This issue was also discussed under BUG Appeal point 2.1. In summary, Ross Dent, for NICE, said that paragraph 3.8 of the FAD explains that fewer patients in both STAMPEDE and LATITUDE had follow-on treatment for hormone-relapsed disease after ADT alone than would occur in NHS clinical practice.

176. The Appeal Panel noted the substantial difference in the use of follow-on abiraterone between the STAMPEDE trial and the company's estimate of current practice, and judged that it was reasonable to conclude that the magnitude of overall survival benefit of abiraterone may be over-estimated. They were satisfied that the Committee had given clear reasons for the statement referred to in the appeal point, both in the FAD and during the hearing. The Panel were not persuaded that either the similar results in two abiraterone trials or the similar OS benefit of enzalutamide should alter this conclusion.

177. The Appeal Panel therefore dismissed the appeal on this point.

**BUG Appeal point Ground 2.6:** Point 7 The statement "*Neither STAMPEDE nor LATITUDE likely capture all the benefit on overall survival of follow-on treatments used in NHS clinical practice*" is unreasonable.

178. The Panel noted that this appeal point was difficult to distinguish from BUG appeal point 2.1. The two were considered together at the hearing. The discussion of BUG appeal point 2.1 in this letter captures all relevant considerations.

179. The Appeal Panel therefore dismissed the appeal on this point.

### ***Appeal by Janssen***

**Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.**

**Janssen Appeal point Ground 2.1:** The Appraisal Committee's conclusion that "*there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination*" is unreasonable in the context of the available evidence.

180. Mohamed Lockhat, for Janssen, said that oncologists are making decisions on a day-to-day basis about which patients can receive docetaxel. The NHSE commissioning policy for docetaxel also provides clear criteria to operationalise this. The Blueteq criteria from NHSE proposed at the third Committee meeting also provide a workable set of criteria.

181. Professor Adler, for the appraisal committee, said that there are relatively few patients who *cannot* take docetaxel and this is clear in the marketing authorisation. There are other patients who *should not* take docetaxel, including those with relative contra-indications or an ECOG score greater than or equal to 3. The Committee were not presented with evidence on abiraterone in these groups, because LATITUDE randomised chemo-fit men. She noted clinical expert opinion that fitness for docetaxel is not clear cut or easy to operationalise. She quoted Professor James'

comment at the hearing, describing this definition as “slippery” and his previous comment in an email about a “larger number who are chemo-borderline”.

182. Dr Latimer, for the appraisal committee, said the appraisal committee were not presented with any evidence of the efficacy of abiraterone in those unfit for chemotherapy. If chemotherapy-unfit patients were included in the STAMPEDE and LATITUDE trials, the Committee were never presented with an analysis on these patients. In addition, the Committee was never presented with a cost-effectiveness analysis that excluded docetaxel from the treatment pathway. The company provided a model said to relate to chemotherapy-ineligible patients, but this modelled a large proportion of patients in both groups receiving docetaxel after relapse.
183. Dr Latimer stated that the Committee did consider ICERs for abiraterone versus ADT alone. These ICERs were still much higher than the range usually considered a cost-effective use of NHS resources. He said that the Committee did not ignore the chemotherapy-unfit group, but just were not provided with any evidence or analyses for that group.
184. Dr Williams, for Janssen, argued that this does not address the central question of how it can be reasonable to say a population cannot be defined when it has previously been defined.
185. Professor Adler, for the appraisal committee, said that it would be irrational to approve a technology for a group where there were no data and not approve that technology for a group where there were data. She said that doctors have a sense of who would not do well with chemotherapy, but this can nevertheless be difficult to define. She acknowledged that this could have been articulated more clearly in the FAD.
186. Dr Patel, for the appraisal committee, said the Committee were aware of the need to operationalise any definition in a way that could be applied consistently in clinical practice and they had heard from clinical experts that this was difficult. This clinical opinion came over very strongly at the time of the Committee meeting.
187. Professor Adler, for the appraisal committee, said that the challenge was not simply to define men who couldn't take docetaxel, but those could take abiraterone but not docetaxel.
188. Professor James, for BUG, said that there is not a hard criterion to define who is fit for chemotherapy. The increase in recruitment rate to the STAMPEDE trial when the docetaxel arm closed demonstrates that clinicians can identify patients who cannot have docetaxel but are suitable for abiraterone.
189. The Panel concluded as follows - NICE processes expect Committees to start by considering a technology's cost-effectiveness in the whole population covered by the marketing authorisation. However, where the technology is not cost-effective in the whole population, recommendations can be made for sub-groups. To do so, a Committee would need to first define the sub-group, then see evidence for that sub-group, and then make a judgement on cost-effectiveness. This appeal point was

concerned with the first stage of that process: whether it was possible to define a sub-group of men who are not eligible for docetaxel.

190. The Panel was satisfied that the Committee took reasonable steps to obtain relevant evidence on this question, including considering expert evidence and other attempts to define this sub-group. However, the Panel were concerned that there was insufficient reasoning for the Committee's conclusion that this sub-group could not be defined. Given that clinical criteria to define eligibility for docetaxel do exist, the Panel judged that a reasonable Committee should give clear reasons why these criteria were not suitable in the current appraisal. As discussed under appeal point Janssen 1a2c, the Panel judged that the FAD did not adequately explain the reasons why the approach used in the Radium appraisal was not considered suitable here. The Panel heard that the Committee were concerned that no evidence had been presented on the use of abiraterone in men who were not fit for docetaxel. However, the Panel judged that this was a different issue from the question of whether the subgroup of patients unfit for docetaxel could be defined.

191. The Appeal Panel therefore upheld the appeal on this point.

192. The Institute should explicitly consider whether it is possible to define a group of patients who are ineligible/unsuitable for docetaxel, before going on to consider whether there is evidence available for the effectiveness and cost-effectiveness of abiraterone in that group. If it concludes that approaches taken in other settings are not suitable in this appraisal, it should give clear reasons for this.

**Janssen Appeal point Ground 2.2:** The Appraisal Committee's conclusion that the benefits of abiraterone may be different in those patients who are unable to receive docetaxel is unreasonable in light of the evidence available

193. This point was discussed at the hearing together with BUG appeal point 2.2 and Janssen appeal point 1a3. The account of the discussion during the hearing should be read alongside these sections of the decision letter, but each point was considered separately by the Panel.

194. Mohamed Lockhat, for Janssen, said that there was no plausible biological reason why the effect of abiraterone would be any different in patients ineligible for chemotherapy. The mechanism of action of abiraterone is completely different from that of docetaxel.

195. As discussed under BUG appeal point 2.2, Professor James, for BUG, agreed that there is no reason to think that abiraterone works less well in a chemotherapy-unfit population. He explained that when the docetaxel arm of STAMPEDE closed, chemotherapy-unfit men were probably being randomised but this did not seem to affect the efficacy or safety of abiraterone.

196. Dr Latimer, for the appraisal committee, acknowledged that some chemotherapy-unfit patients were probably recruited after the docetaxel arm of the trial closed in 2013. However, comparing hazard ratios before and after 2013 is not a chemotherapy fit v unfit comparison. The Committee were not presented with any



evidence on the effectiveness of abiraterone specifically in patients unable to take docetaxel. In addition, the Committee were never presented with a cost-effectiveness analysis that excluded docetaxel from the treatment pathway. (The company provided a model said to relate to chemotherapy-ineligible patients, but this modelled a large proportion of patients in both groups receiving docetaxel after relapse.) He also said that there is some trial data to suggest that abiraterone may be less effective in older patients or those with higher ECOG scores (greater frailty). Despite this, the Committee did consider ICERs for abiraterone versus ADT alone (a proxy for the chemotherapy-ineligible group) and this modelling assumed that abiraterone is equally effective in this group.

197. Dr Latimer emphasised that the Committee did not say that the benefits of abiraterone *are* different in those who are unable to take docetaxel, but simply that we don't know because the Committee were not presented with the evidence. He argued that the statement in the FAD is not just reasonable but irrefutable.
198. Mohamed Lockhat, for Janssen, said that the company cannot be expected to do trials in every possible sub-population. The Committee need to say what is the standard of care for men who are ineligible for chemotherapy. It is clear that this is ADT alone, and we have evidence for the effectiveness of abiraterone versus ADT alone.
199. Professor Adler, for the appraisal committee, also emphasised that the FAD does not say that the benefits of abiraterone are different in chemotherapy-ineligible men, just that we do not know if they are the same. The Committee were aware that chemotherapy-ineligible men are likely to have co-morbidities, and it is reasonable that these co-morbidities could be effect modifiers. She also pointed out that the FAD does consider the comparison of abiraterone with ADT alone (as a proxy for the chemotherapy-ineligible group), and indeed assumes equal efficacy in this group.
200. Dr Latimer, for the appraisal committee, said that patients ineligible for chemotherapy are more likely to have and ECOG scores of 3 or more. These patients would be expected to have shorter survival, so the trials may over-estimate benefit in this group. He recalled that Peter Clark, of the Cancer Drugs Fund, had highlighted the fact that 98% of patients in LATITUDE had ECOG scores of 0-1. These patients were very fit, and therefore likely to tolerate treatment better than "all comers" in NHS clinical practice.
201. Professor James, for BUG, replied that most men with ECOG scores of 3 or more would not be suitable for abiraterone either. He said that fitness for chemotherapy is multi-factorial, and not defined simply by ECOG score.
202. Dr Latimer, for the appraisal committee, said that the reason the FAD sets out the uncertainties in the data is because the company had submitted an analysis they said was specifically for a chemotherapy-ineligible population. The FAD therefore had to make the thinking of the Committee clear.
203. The Appeal Panel concluded that the FAD expresses uncertainty about the benefits of abiraterone in a chemotherapy-ineligible population rather than saying

that the benefits are different. The Panel accepted that the Committee were not presented with any evidence on the effectiveness of abiraterone specifically in this group. Whilst it may have been reasonable to judge (based on biological plausibility) that the effect would be the same, it was also reasonable to consider that the effect could be different (as co-morbidities or frailty could be effect-modifiers). In fact, when the Committee modelled the cost-effectiveness of abiraterone versus ADT alone (as a proxy for the chemotherapy-ineligible population) they did assume equal efficacy in this group. The Panel judged that it was reasonable for the FAD to have set out areas of uncertainty in the data.

204. The Appeal Panel therefore dismissed the appeal on this point.

## **Conclusion and effect of the Appeal Panel's decision**

205. The Appeal Panel therefore upholds the appeal on the following grounds:

**PCUK/TPC Appeal Ground 1a.1:** In making the assessment that preceded the recommendation, NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.

**BUG Appeal Ground 1a.3:** That the failure of the Committee to consider the STAMPEDE group's recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision.

**Janssen Appeal Ground 1a.2c:** The Appraisal Committee's conclusion that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" does not: (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223.

**Janssen Appeal Ground 1a.4:** The conclusions of the Appraisal Committee in relation to the cost-effectiveness of abiraterone in this appraisal are opaque.

(insofar as it relates to the failure to provide an ICER range.)

**PCUK/TPC Appeal point Ground 2.1:** The recommendation is unreasonable in the light of the evidence submitted to NICE concerning the effectiveness of abiraterone in patients who cannot receive docetaxel.

**Janssen Appeal point Ground 2.1:** The Appraisal Committee's conclusion that "there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination" is unreasonable in the context of the available evidence.

206. The appeal is dismissed on all other grounds.

207. The appraisal is remitted to the appraisal committee who must now take all reasonable steps to address these points, as set out under the individual appeal points above.

208. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may

be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of NICE publishing the final guidance.

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

**ERG critique of additional data submitted to NICE post-appeal**

**Produced by** Aberdeen HTA Group

**Date Completed** 27 November 2020

**Contains** ■ information

This report provides the ERG’s commentary and critique of further evidence submitted to NICE in support of Appeals lodged by the British Uro-Oncology Group, Prostate Cancer UK and Tackle Prostate Cancer, and Janssen against the FAD on abiraterone for treating newly diagnosed metastatic hormonenaïve prostate cancer [ID945].

As detailed in the appeal decision letter, the appeal panel upheld the appeal on following grounds, and detailed further actions for NICE outlined in Table 1.

**Table 1 Upheld grounds for appeal**

<b>Appeal points upheld as detailed in the appeal decision letter</b>	<b>Actions for NICE as detailed in the appeal decision letter</b>
“ <b>PCUK/TPC Appeal Ground 1a.1:</b> In making the assessment that preceded the recommendation, NICE has failed to act fairly by neglecting to consider inequalities of healthcare provision caused by its decision.”	“... the Institute must have in mind the fact that older men are over-represented in the chemo-ineligible subgroup when it considers the possibility of defining and making a recommendation for this subgroup.”
“ <b>BUG Appeal Ground 1a.3:</b> That the failure of the Committee to consider the STAMPEDE group’s recently presented quality of life data and/or COVID-19 resulted in a discriminatory decision.”	“... the Institute must have in mind the fact that older men are over-represented in the chemo-ineligible subgroup when it considers the possibility of defining and making a recommendation for this subgroup.”
“ <b>Janssen Appeal Ground 1a.2c:</b> The Appraisal Committee’s conclusion that “ <i>there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination</i> ” does not: (c) provide reasons for deviating from its conclusions in the earlier appraisal of Radium-223.”	“The Institute should now explicitly consider the question of whether the approach used in the radium appraisal to define a sub-group of patients ineligible for docetaxel could also be used in this appraisal. If it concludes that it cannot use this approach, the reasons for this should be clearly stated”
“ <b>Janssen Appeal Ground 1a.4:</b> The conclusions of the Appraisal Committee in relation to the cost-effectiveness of abiraterone in this appraisal are opaque. (insofar as it relates to the failure to provide an ICER range.)	“The Institute must now consider whether it is possible to give any more precise indication of the ICERs calculated, while not compromising the confidentiality of competitor pricing. For example, a range might be given, within which the actual ICER falls. How broad or narrow the range would have to be to preserve confidentiality would depend on the model, and the Panel cannot take a view.”
“ <b>PCUK/TPC Appeal point Ground 2.1:</b> The recommendation is unreasonable in the light of the evidence submitted to NICE concerning the effectiveness of abiraterone in patients who cannot receive docetaxel.	“The Institute should explicitly consider whether it is possible to define a group of patients who are ineligible and/or unsuitable for docetaxel, before going on to consider whether there is evidence available for the effectiveness and cost-effectiveness of abiraterone in that group. If it concludes that approaches taken in other settings are not suitable in this appraisal, it should give clear reasons for this”
“ <b>Janssen Appeal point Ground 2.1:</b> The Appraisal Committee’s conclusion that “there are no clear-cut clinical criteria to define who can have abiraterone in combination but not docetaxel in combination” is unreasonable in the context of the available evidence.”	“The Institute should explicitly consider whether it is possible to define a group of patients who are ineligible/unsuitable for docetaxel, before going on to consider whether there is evidence available for the effectiveness and cost-effectiveness of abiraterone in that group. If it concludes that approaches taken in other

	settings are not suitable in this appraisal, it should give clear reasons for this.”
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In support of their appeals, the appellants, BUG, Prostate Cancer UK and Tackle Prostate Cancer, submitted various published and unpublished documents to NICE as detailed below (Table 2)

**Table 2 Summary of documents/files submitted in support of Appeal grounds**

<b>Content of documents received</b>	<b>Reference</b>
<p>Long-term survival results from the STAMPEDE trial for the comparison of docetaxel plus ADT versus ADT alone in those with high burden and low burden metastatic disease.</p> <p>Long-term OS analysis, data cut off 13 July 2018, median follow-up of 78.2 months</p>	<p>Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial [published correction appears in Ann Oncol. 2020 Mar;31(3):442]. Ann Oncol. 2019;30(12):1992-2003.</p>
<p>Results of the STAMPEDE trial for the comparison of abiraterone plus ADT and ADT alone. Including a break down by those with metastatic and non-metastatic disease.</p> <p>Data cut off, February 10, 2017, Median follow-up 40 months.</p>	<p>James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338-351.</p>
<p>Results of the STAMPEDE trial for the comparison of Abiraterone plus ADT versus ADT alone in those with “High-” and “Low-risk” Metastatic hormone sensitive prostate cancer.</p> <p>Overall survival and failure free survival data for the relevant subgroups from the 10 February 2017 data cut, Median follow-up 42 months</p>	<p>Hoyle AP, Ali A, James ND, et al. Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019 Dec;76(6):719-728.</p>
<p>Long-term results from STAMPEDE for the comparison of abiraterone plus ADT versus ADT alone.</p> <p>Includes OS in high risk and low risk mHSPC.</p> <p>Data cut 3 April 2020, 3 years after primary analysis, Median follow-up 6.1 years.</p>	<p>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). ESMO Virtual Congress, 2020</p>
<p>Final overall survival analysis for the LATITUDE trail comparing Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer</p> <p>Data cut-off Aug 15, 2018, median follow-up 51.8 months</p>	<p>Fizazi K, Tran N, Fein L, 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.</p>
<p>Cost-effectiveness analysis paper on abiraterone plus ADT versus ADT alone for newly diagnosed advanced prostate cancer, based on data from the STAMPEDE trial. Including results for those with metastatic disease at baseline.</p>	<p>Unpublished manuscript</p>
<p>Paper on the quality of life (QLQ-C30) for men with prostate cancer contemporaneously</p>	<p>Unpublished manuscript</p>

<p>randomly allocated to receive either docetaxel or abiraterone in STAMPEDE</p> <p>Quality of life data over two years in patients with HSPC, with results also presented separately for those with metastatic and non-metastatic disease.</p>	
<p>Chemotherapy uptake data (Excel spreadsheet) in incident metastatic prostate cancer by age.</p>	<p>Summary data based on patient-level information collected by the NHS. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE).</p>

The published papers from STAMPEDE have been seen before as part of the company's previous submissions. This commentary/critique therefore focusses primarily on the new evidence not previously seen by the committee: 1) The long-term follow-up of the STAMPEDE trial comparison of abiraterone plus ADT versus ADT alone (James et al., 2020); 2) the unpublished cost-effectiveness analysis of abiraterone plus ADT versus ADT alone based on STAMPEDE data; 3) and the unpublished quality of life data in patients contemporaneously randomised to receive ADT plus docetaxel or ADT plus abiraterone plus prednisolone; and 4) The NHS data on chemotherapy uptake in incident metastatic prostate cancer by age. Consideration is given throughout to whether the new evidence helps address any of the actions for the upheld grounds for appeal.

### **1. Long-term follow-up of the STAMPEDE abiraterone plus ADT versus ADT comparison**

The slide set that was shared provides data on overall survival, failure free survival, and SREs out to 8 years (median 6.1 years follow-up). The notable highlight from this data is that the relative efficacy of abiraterone plus ADT versus ADT alone is maintained from the earlier follow-up. For overall survival in the high-risk metastatic subgroup, the hazard ratio is reported to be 0.54 (95% CI; 0.43 to 0.69) compared to 0.54 (95% CI; 0.41 – 0.7) at median follow-up of 3.3 years ( Hoyle et al. 2019). Based on the presented OS Kaplan Maier curves, [REDACTED]. Thus, this would support cost-effectiveness modelling assumptions that maintain relative treatment effects up to and beyond 8 years. Nevertheless, there are remaining uncertainties regarding discrepancies between the distribution of subsequent treatments used in STAMPEDE and the distribution of subsequent treatment in the current care pathway.

With respect to PCUK/TPC Appeal point Ground 2.1, uncertainties remain around the applicability of the survival curves and the relative treatment effects (hazard ratios) from the STAMPEDE and LATITUDE trials to a docetaxel ineligible population. Points are summarised in the appeal decision letter which suggest that following closure of recruitment to the docetaxel arm of STAMPEDE, recruitment to the trial increased, suggesting that clinicians were able to identify patients who were suitable for randomisation to abiraterone, who would not have been randomised to docetaxel. It is further noted that following this increase in recruitment, the hazard ratio improved despite the increase in age of the enrolled population. Whilst it is acknowledged that chemo-ineligible men are likely to be older, comparing the pre and post 2013 hazard ratio from STAMPEDE is not the same a subgroup analysis of chemo eligible and chemo-ineligible patients. The STAMPEDE publications do



not identify a specific sub-population of patients who would be considered ineligible for docetaxel.

It is further noted in the appeal decision letter that efficacy with respect to OS may be diluted in older men when competing risks of death are higher, and so progression free survival is a better measure of whether abiraterone has similar efficacy in older and younger men. This appears to be in keeping with the subgroup analysis reported in James et al. (2017).

**2. Cost-effectiveness analysis of abiraterone plus ADT versus ADT alone based on STAMPEDE data**

The unpublished cost-effectiveness paper that was shared [REDACTED]  
[REDACTED]  
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Bearing these limitations in mind, the unpublished model produces results that are broadly in keeping with the company's model, in that it projects substantial life year and QALY gains for abiraterone plus ADT versus ADT alone.

[REDACTED]  
[REDACTED]

[REDACTED] This is perhaps to be expected given the difference in populations.

However, comparing against the latest OS Kaplan Meier data for the high risk mHSPC subgroup of STAMPEDE (James et al., 2020),

[REDACTED], suggesting that the Company's Weibull extrapolation may be conservative. Therefore, considering cost-effectiveness modelling assumptions in relation to Janssen Appeal Ground 1a.4, the latest data from STAMPEDE appears to support the company's log-logistic curves for the high-risk mHSPC cohort as a whole.

With respect to a chemotherapy ineligible population, it is likely that curves base on STAMPEDE or LATIDUE will overestimate PFS and OS, assuming chemo ineligible patients are at a greater risk of death from other causes compared to those recruited to the trials.

**3. Quality of life in patients contemporaneously randomised to receive ADT plus docetaxel or ADT plus abiraterone plus prednisolone**

The unpublished quality of life study submitted in support of the appeal reports QLQ-C30 quality of life data over two years for patient contemporaneously randomised between docetaxel plus ADT and Abiraterone plus ADT in the STAMPEDE trial. [REDACTED]

[REDACTED]

The above data provides a useful insight into

[REDACTED]

There are, however, several limitations with respect to informing modelling uncertainties for the current abiraterone appraisal:

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. This is reasonable in keeping the assumptions in the company model, whereby utility on abiraterone is higher in the mHSPC state compared to ADT alone and docetaxel plus ADT, and a further decrement is applied to docetaxel during the on-treatment period.

#### **4. Chemotherapy uptake data**

The final piece of evidence submitted in support to the Appeal provides information on uptake of chemotherapy across age categories of incident metastatic prostate cancer. This is based on patient-level information collected by the NHS, which is collated, maintained and quality assured by the National Cancer Registration and Analysis Service (part of Public Health England).

The data do show a clear negative relationship between increasing age and the percentage of incident metastatic patients receiving chemotherapy. This relevant to the equality argument of PCUK/TPC Appeal Ground 1a.1, that chemo-ineligible patients are likely to disproportionately older than chemo-eligible patients. The data does not give other insights into the characteristics of those patients that did not receive chemotherapy.

## References

Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial [published correction appears in Ann Oncol. 2020 Mar;31(3):442]. Ann Oncol. 2019;30(12):1992-2003.

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Fizazi K, Tran N, Fein L, 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.