Clinical Priorities Advisory Group
20 May 2024

Agenda Item No	6.4
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	2312

Title
Abiraterone acetate and prednisolone for high-risk, hormone sensitive non-metastatic prostate cancer (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
Abiraterone acetate and prednisolone is recommended to be available as an off-label treatment for patients with high-risk, hormone sensitive non-metastatic prostate cancer. Abiraterone acetate is proposed as an addition to current standard of care within the criteria set out in the policy proposition document. This policy proposition is for adults which reflects the age group affected by prostate cancer. Commissioning responsibility for this treatment currently resides with NHS England, however, in time it is expected that this will transfer to Integrated Care Boards.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Deputy Director of Cancer Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In high-risk, non-metastatic hormone sensitive prostate cancer, what is the clinical effectiveness and safety of abiraterone acetate and prednisolone compared with current standard care?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Moderate to low	Overall survival is important to patients as patients with high-risk non-metastatic prostate cancer have a higher mortality rate due to risk of metastasis. Improved survival is an important marker of effective treatment. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to overall survival[1] in patients with high-risk, non-metastatic prostate cancer. This RCT compared abiraterone acetate and prednisolone (AAP) plus androgen deprivation therapy (ADT) to ADT at median 40[2] and 85 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at median 48[3] months follow-up. **At median 85 months follow-up:** *AAP & ADT vs ADT* • One RCT (Attard et al 2022) reported *statistically significantly fewer* deaths with AAP & ADT (95/459, 20.7%) compared to ADT (142/455, 31.2%) at a median of 85 months follow-up (HR 0.63 (95%CI 0.48 to 0.82) p=0.005). **(MODERATE)** **At median 40 months follow-up:** *AAP & ADT vs ADT* • One RCT (James et al 2017) reported *no statistically significant difference* in deaths between AAP & ADT (34/460, 7.4%) and ADT (44/455, 9.7%) at a median of 40 months follow-up (HR 0.75 (95%CI 0.48 to 1.18) p not reported). **(MODERATE)** **At median 48 months follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Sydes et al 2018) reported *no statistically significant difference* in deaths between AAP & ADT (16/150, 10.7%) and docetaxel & ADT (6/74, 8.1%) at a median of 85 months follow-up (HR 1.51 (95%CI 0.58 to 3.93) p=0.395). **(LOW)**

	For AAP & ADT vs ADT: One RCT provided moderate certainty evidence of statistically significantly fewer deaths for AAP & ADT compared to ADT at a median of 85 months follow-up. There was moderate certainty evidence of no statistically significant difference in deaths at a median of 40 months follow-up. **For AAP & ADT vs docetaxel & ADT: One RCT provided low certainty evidence of no statistically significant difference in deaths between AAP & ADT and docetaxel & ADT at a median of 48 months follow-up.**
Metastasis-free survival **Certainty of evidence:** High to low	Metastasis-free survival is important to patients because high-risk prostate cancer has a high-risk of metastasis which confers a worse prognosis. Metastatic-free survival indicates that the intervention is impacting disease progression. Metastases cause symptoms such as bone pain so this confers a quality-of-life impact. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to metastasis-free survival[4] in patients with high-risk, non-metastatic prostate cancer. This RCT compared AAP plus ADT to ADT at a median of 85 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at a median of 48 months follow-up. **At median 85 months follow-up:** *AAP & ADT vs ADT* • One RCT (Attard et al 2022) reported *statistically significantly fewer* metastasis-free survival events with AAP & ADT (111/459, 24.2%) compared to ADT (183/455, 40.2%) at a median of 85 months follow-up (HR 0.54 (95%CI 0.43 to 0.68) p<0.0001). **(HIGH)** **At median 48 months follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Sydes et al 2018) reported *no statistically significant difference* in metastasis-free survival events between AAP & ADT (18/150, 12.0%) and docetaxel & ADT (10/74, 13.5%) at a median of 48 months follow-up (HR 0.91 (95%CI 0.42 to 2.01) p=0.824). **(LOW)** **For AAP & ADT vs ADT: One RCT provided high certainty evidence of statistically significantly fewer metastasis-free survival events for AAP & ADT compared to ADT at a median of 85 months follow-up.** **For AAP & ADT vs docetaxel & ADT: One RCT provided low certainty evidence of no statistically significant difference in metastasis-free survival events between AAP & ADT and docetaxel & ADT at a median of 48 months follow-up.**
Progression free survival **Certainty of evidence:** High to low	Progression free survival is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to progression free survival in patients with high-risk, non-metastatic prostate cancer. This RCT compared AAP plus ADT to ADT at a median of 40 and 85 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at a median of 48 months follow-up. This outcome was reported as failure-free survival[5] and progression free survival[6]. **At median 85 months follow-up:**

	AAP & ADT vs ADT • One RCT (Attard et al 2022) reported *statistically significantly fewer* failure-free survival events with AAP & ADT (120/459, 26.1%) compared to ADT (277/455, 51.0%) at a median of 85 months follow-up (HR 0.39 (95%CI 0.31 to 0.49) p not reported). **(HIGH)** • One RCT (Attard et al 2022) reported *statistically significantly fewer* progression free survival events with AAP & ADT (84/459, 18.3%) compared to ADT (166/455, 36.5%) at a median of 85 months follow-up (HR 0.43 (95%CI 0.33 to 0.56) p not reported). **(HIGH)** **At median 40 months follow-up:** *AAP & ADT vs ADT* • One RCT (James et al 2017) reported *statistically significantly fewer* failure-free survival events with AAP & ADT (38/460, 8.3%) compared to ADT (142/455, 31.2%) at a median of 40 months follow-up (HR 0.21 (95%CI 0.15 to 0.31) p not reported). **(HIGH)** **At median 48 months follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Sydes et al 2018) reported *statistically significantly fewer* failure-free survival events with AAP & ADT (13/150, 8.7%) compared to docetaxel & ADT (18/74, 24.3%) at a median of 48 months follow-up (HR 0.34 (95%CI 0.16 to 0.69) p=0.003). **(MODERATE)** • One RCT (Sydes et al 2018) reported *no statistically significant difference* in progression free survival events between AAP & ADT (9/150, 6.0%) and docetaxel & ADT (10/74, 13.5%) at a median of 48 months follow-up (HR 0.42 (95%CI 0.17 to 1.05) p=0.064). **(LOW)** **For AAP & ADT vs ADT: One RCT provided high certainty evidence of statistically significantly fewer failure-free survival events for AAP & ADT compared to ADT at a median of 40 and 85 months follow-up. The same RCT also provided high certainty evidence of statistically significantly fewer progression free survival events for AAP & ADT compared to ADT at a median of 85 months follow-up.** **For AAP & ADT vs docetaxel & ADT: One RCT provided moderate certainty evidence of statistically significantly fewer failure-free survival events for AAP & ADT compared to docetaxel & ADT at a median of 48 months follow-up. There was low certainty evidence of no statistically significant difference in progression free survival between AAP & ADT and docetaxel & ADT at a median of 48 months follow-up.**
Important outcomes	
Quality of life (QoL) **Certainty of evidence:** Low	Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to quality of life in patients with high-risk, non-metastatic prostate cancer. Quality of life was reported in one paper reporting a comparison of AAP plus ADT and docetaxel plus ADT at 2 years follow-up. No evidence was identified comparing AAP & ADT to ADT for quality of life. Quality of life was assessed using the EORTC QLQ-C30 version 3[7]. The pre-defined

	criterion for a clinically meaningful difference in global-quality of life was >4.0 points. **At 2 years follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Rush et al 2022) reported *no statistically significant difference* in global-quality of life score between AAP & ADT (n=137) and docetaxel & ADT (n=71) at 2 years follow-up (difference 3.0 points (favouring AAP & ADT) (95%CI -2.4 to 8.3) p=0.275)[8]. Individual group scores were only presented graphically. **(LOW)** **For AAP & ADT vs ADT: No evidence identified** **For AAP & ADT vs docetaxel & ADT: One RCT provided low certainty evidence of no statistically significant difference in global-quality of life between AAP & ADT and docetaxel & ADT at 2 years follow-up.**
Symptom alleviation **Certainty of evidence:** Low to very low	Symptom alleviation is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to symptom alleviation in patients with high-risk, non-metastatic prostate cancer. This RCT compared AAP plus ADT to ADT at median 40 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at median 48 months follow-up. This outcome was reported as number of symptomatic skeletal events[9]. **At median 40 months follow-up:** *AAP & ADT vs ADT* • One RCT (James et al 2017) reported *no statistically significant difference* in symptomatic skeletal events between AAP & ADT (11/460, 2.4%) and ADT (1/455, 4.2%) at a median of 40 months follow-up (HR 0.56 (95%CI 0.27 to 1.18) p not reported). **(LOW)** **At median 48 months follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Sydes et al 2018) reported *no statistically significant difference* in symptomatic skeletal events between AAP & ADT (5/150, 3.3%) and docetaxel & ADT (2/74, 2.7%) at a median of 48 months follow-up (HR 1.28 (95%CI 0.24 to 6.67) p=0.771). **(VERY LOW)** **For AAP & ADT vs ADT: One RCT provided low certainty evidence of no statistically significant difference in symptomatic skeletal events between AAP & ADT and ADT at a median of 40 months follow-up.** **For AAP & ADT vs docetaxel & ADT: One RCT provided very low certainty evidence of no statistically significant difference in symptomatic skeletal events between AAP & ADT and docetaxel & ADT at a median of 48 months follow-up.**
Prostate cancer-specific survival **Certainty of evidence:** High to low	Prostate cancer-specific survival looks specifically at death due to prostate cancer. This is an important outcome to consider as prostate cancer affects patients of an older age group who may have other medical conditions. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to prostate cancer-specific survival[10] in patients with high-risk, non-metastatic prostate cancer. This RCT compared AAP plus ADT to ADT at median 85 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at a median of 48 months follow-up.

	At median 85 months follow-up: *AAP & ADT vs ADT* • One RCT (Attard et al 2022) reported *statistically significantly fewer* prostate cancer-specific deaths with AAP & ADT (48/459, 10.5%) compared to ADT (86/455, 18.9%) at a median of 85 months follow-up (HR 0.52 (95%CI 0.36 to 0.75) p not reported). **(HIGH)** **At median 48 months follow-up:** *AAP & ADT vs docetaxel & ADT* • One RCT (Sydes et al 2018) reported *no statistically significant difference* in prostate cancer-specific deaths between AAP & ADT (6/150, 4.0%) and docetaxel & ADT (4/74, 5.4%) at a median of 48 months follow-up (HR 0.82 (95%CI 0.24 to 2.81) p=0.751). **(LOW)** **For AAP & ADT vs ADT: One RCT provided high certainty evidence of statistically significantly fewer prostate cancer-specific deaths for AAP & ADT compared to ADT at a median of 85 months follow-up.** **For AAP & ADT vs docetaxel & ADT: One RCT provided low certainty evidence of no statistically significant difference in prostate cancer-specific deaths between AAP & ADT and docetaxel & ADT at a median of 48 months follow-up.**
Safety	
Safety outcomes **Certainty of evidence:** Moderate to low	Safety outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, one multi-arm, multi-stage platform RCT (STAMPEDE) provided evidence relating to safety in patients with high-risk, non-metastatic prostate cancer. Safety outcomes were reported in one paper comparing AAP plus ADT and ADT at 24 months follow-up. No evidence was identified comparing AAP & ADT to docetaxel & ADT for non-metastatic patients. Safety outcomes were reported as adverse events[11] and reasons for permanently stopping AAP. **At 24 months follow-up:** *AAP & ADT vs ADT* • One RCT (Attard et al 2022) reported the number of adverse events ≥Grade 3 with AAP & ADT (169/451, 37.5%) and ADT (130/455, 28.6%) at 24 months follow-up. The groups were not statistically compared. **(MODERATE)** • One RCT (Attard et al 2022) reported the number of Grade 5 adverse events with AAP & ADT (3/451, 0.7%) and ADT (0/455, 0%) at 24 months follow-up. The groups were not statistically compared. **(LOW)** • One RCT (Attard et al 2022) reported that at 24 months the Grade 4 adverse events with AAP & ADT were ALT increased, hypokalaemia and anaemia. Grade 4 adverse events with ADT were anaemia. • One RCT (Attard et al 2022) reported that at 24 months, the most common (≥5%) Grade 3 adverse events in the AAP & ADT group were erectile dysfunction (9%), hypertension (5%) and ALT increased (5%). The most common (≥5%) Grade 3 adverse event in the ADT group was erectile dysfunction (11%). • One RCT (Attard et al 2022) reported that at 24 months, the most common (≥20%) Grade 1-2 adverse events in the AAP & ADT group were fatigue (66%), erectile dysfunction (46%), anaemia

	(41%), insomnia (29%), constipation (28%), hypertension (24%) and cough (23%). The most common (≥20%) Grade 1/2 adverse events in the ADT group were fatigue (61%), erectile dysfunction (46%), anaemia (31%), insomnia (28%) and constipation (23%). • One RCT (Attard et al 2022) reported reasons for permanently stopping AAP (n=451) at 24 months follow-up as treatment complete (59%), excessive toxicity (13%), treatment refusal (3%), disease progression (4%), patient choice (1%), death (1%), clinician decision (1%), intercurrent illness (<1%), not stopped (4%) and other (not further defined) (14%). (**LOW**) **For AAP & ADT vs ADT: One RCT provided moderate to low certainty evidence about the number and type of adverse events of different severity grades with AAP & ADT and ADT at 24 months follow-up. Adverse events ≥Grade 3 were experienced by 37.5% of AAP & ADT patients and 28.6% ADT patients. The groups were not statistically compared. 13% of patients permanently stopped AAP due to excessive toxicity.** **For AAP & ADT vs docetaxel & ADT: No evidence identified**
Abbreviations AAP: Abiraterone acetate and prednisolone; ADT: Androgen deprivation therapy; ALT: Alanine aminotransferase; CI: Confidence intervals; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: Hazard ratio; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy	

In high-risk, non-metastatic hormone sensitive prostate cancer, what is the cost effectiveness of abiraterone acetate and prednisolone compared with current standard care?

Outcome	Evidence statement
Cost effectiveness	In total, one analysis provided evidence for the cost effectiveness of AAP plus ADT compared to ADT in patients with high-risk, non-metastatic prostate cancer, using data from the STAMPEDE trial with median follow-up of 3.08 years. The analysis used a Markov model with a lifetime (45 year) time horizon and used an English NHS perspective using the 2017/2018 published price of abiraterone acetate[12]. No evidence for non-metastatic patients was identified comparing cost effectiveness for AAP & ADT to docetaxel & ADT. **Lifetime time horizon:** *AAP & ADT vs ADT* • One analysis (Clarke et al 2022) reported that AAP & ADT is not cost effective compared to ADT (ICER £149,748 per QALY gained (95% CI not reported)). The probability of AAP & ADT being cost effective compared to ADT at a threshold of £30,000/ QALY was 2.4%. The authors calculated that the cost of abiraterone acetate would need to be £28/day for the ICER to fall below the £30,000/QALY threshold.
Abbreviations AAP: Abiraterone acetate and prednisolone; ADT: Androgen deprivation therapy; CI: Confidence intervals; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy	

From the evidence selected, are there any subgroups of patients that may benefit from abiraterone acetate and prednisolone more than the wider population of interest?

Outcome	Evidence statement
Subgroups	Patients with non-metastatic disease formed a subgroup within the multi-arm, multi-stage platform STAMPEDE RCT. No other subgroup analyses were reported for patients with non-metastatic disease.
Abbreviations RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy	

From the evidence selected, what are the criteria used by the research studies to define high-risk, non-metastatic hormone sensitive prostate cancer?

Outcome	Evidence statement
Definitions of high risk, non-metastatic hormone sensitive prostate cancer	The STAMPEDE RCT (described in Attard et al 2022) defined patients with high-risk non-metastatic prostate cancer as patients with a WHO performance status of 0 to 2 and no evidence of distant metastasis on conventional imaging. Patients had either: • Node positive disease or • If node-negative, at least 2 of: a tumour stage of T3 or T4, a Gleason score of 8 to 10, a PSA concentration ≥40 ng/mL or • Relapsing disease with high-risk features: ≤12 months of total ADT with an interval of ≥12 months without treatment and PSA ≥4ng/mL with a doubling time of <6 months, or PSA concentration ≥20ng/mL[13] In some descriptions of the STAMPEDE population[14], patients with nodal relapse were also described in the inclusion criteria. Patients were intended for long-term treatment with ADT that started no longer than 12 weeks before randomisation.
Abbreviations ADT: Androgen deprivation therapy; mL: Millilitre; ng: Nanogram; PSA: Prostate specific antigen; RCT: randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; WHO: World Health Organization	

From the evidence selected, what dose of abiraterone acetate and prednisolone was used to treat high-risk, non-metastatic hormone sensitive prostate cancer?

Outcome	Evidence statement
Dose of abiraterone acetate and prednisolone	In the STAMPEDE RCT (Attard et al 2022, James et al 2017, Rush et al 2022, Sydes et al 2018), patients received abiraterone acetate (1,000mg) orally daily. Patients in the 111 UK study sites also received 5mg prednisolone daily (AAP). In the five Swiss study sites patients received 5mg of daily prednisone (rather than prednisolone). Patients also received ADT.
Abbreviations ADT: Androgen deprivation therapy; mg: Milligrams; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; UK: United Kingdom	

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** Patients can have significant fatigue or weakness and dizziness which affects mobility • **ability to provide self-care:** Patients can have moderate problems in washing or dressing • **undertaking usual activities:** Patients can have moderate problems in doing their usual activities with shortness of breath when exercising or being active. • **experience of pain/discomfort:** Patients can have moderate pain or discomfort • **experience of anxiety/depression:** Patients can be moderately anxious or depressed
Further details of impact upon patients: People with prostate cancer commonly experience urinary symptoms, fatigue and pain which may limit their exercise tolerance and daily activities including self-care and physical exercise. With progressive disease patients may experience worsening symptoms, in addition to symptoms related to metastatic spread, causing more difficulties in participating in their daily activities and may require additional support from carers. Many people suffer with anxiety as a result of their diagnosis and the risk of recurrence. Some people experience severe anxiety and depression which has the potential to significantly decrease their quality of life and ability to do normal tasks. **Further details of impact upon carers:** Prostate cancer can lead to a moderate burden on carers, who may need to assist the individual with self-care tasks and daily activities. Mental health problems as a consequence of their diagnosis may also affect the relationship between the patient and their family/carers.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This clinical commissioning policy proposition recommends abiraterone acetate and prednisolone for adults with high-risk, hormone sensitive non-metastatic prostate cancer. The recommendation is outside of the marketing authorisation for abiraterone acetate so use is off-label and Trust policy regarding unlicensed medicines should apply. Abiraterone acetate is on the NHS Payment Scheme Annex A, that is, it is an excluded drug.
Considerations from review by National Programme of Care
The proposal received the full support of the Cancer PoC on the 9 May 2024.