NHS England evidence review:

Abiraterone acetate and prednisolone for high-risk, hormone sensitive non-metastatic prostate cancer

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Abiraterone acetate and prednisolone for high-risk, hormone sensitive non-metastatic prostate cancer

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of abiraterone acetate and prednisolone compared to current standard care for the treatment of high-risk, non-metastatic hormone sensitive prostate cancer.

Patients with high-risk, non-metastatic hormone sensitive prostate cancer may include newly diagnosed patients and those with relapsing prostate cancer with high-risk features.

Abiraterone acetate is an anti-androgen treatment that is licenced in adults for the treatment of metastatic prostate cancer. It works by inhibiting enzymes involved in the testosterone production pathway, thus reducing circulating levels of testosterone. It is administered orally in combination with prednisolone in a once daily regime.

Current standard care is either androgen deprivation therapy (ADT) or ADT and docetaxel chemotherapy, and patients may or may not also receive radiotherapy. ADT works by lowering the level of systemic androgenic hormones such as testosterone.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from abiraterone acetate and prednisolone more than others, the criteria used by the included studies to define high-risk, non-metastatic hormone sensitive prostate cancer and the dose of abiraterone acetate and prednisolone that was used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of abiraterone acetate and prednisolone compared to current standard care for the treatment of high-risk, non-metastatic hormone sensitive prostate cancer. The searches for evidence published since January 2013 were conducted on 29th June 2023 and 26th July 2023[1] and identified 1,614 potential references. These were screened using their titles and abstracts and 27 full text papers potentially relating to the use of abiraterone acetate and prednisolone for high-risk, non-metastatic hormone sensitive prostate cancer were obtained and assessed for relevance.

One multi-arm, multi-stage, multi-centre platform randomised controlled trial (RCT) (STAMPEDE) (published in four papers) was identified for inclusion. This trial was predominantly conducted in UK centres. Two papers (Attard et al 2022, James et al 2017) compared abiraterone acetate and prednisolone (AAP) plus androgen deprivation therapy (ADT) (n=460[2]) to ADT (n=455) in patients with high-risk, non-metastatic prostate cancer. Median follow-up in the papers was 85 months and 40[3] months respectively. A third paper (Sydes et al 2018) reported a comparison of AAP plus ADT (n=150) and docetaxel plus ADT (n=74) in patients with high-risk, non-metastatic prostate cancer at median 48[4] months follow-up. The fourth paper (Rush et al 2022) reported quality of life for AAP plus ADT (n=137) compared to docetaxel plus ADT (n=71) in patients with high-risk, non-metastatic prostate cancer at two years follow-up.

A fifth paper (Clarke et al 2022) reported cost effectiveness for AAP plus ADT compared to ADT in patients with high-risk, non-metastatic prostate cancer using data from the STAMPEDE trial (at median follow-up of three years). No evidence relating to cost effectiveness was identified for AAP plus ADT compared to docetaxel plus ADT.

In terms of clinical effectiveness:

- **Overall survival[5] (critical outcome).**
  - *For AAP & ADT vs ADT:* One RCT provided moderate certainty evidence of statistically significantly fewer deaths for AAP & ADT (21%) compared to ADT (31%) 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 (7% vs 10%).
  - *For AAP & ADT vs docetaxel & ADT:* One RCT provided low certainty evidence of no statistically significant difference in deaths between AAP & ADT (11%) and docetaxel & ADT (8%) at a median of 48 months follow-up.

- **Metastasis-free survival[6] (critical outcome).**
  - *For AAP & ADT vs ADT:* One RCT provided high certainty evidence of statistically significantly fewer metastasis-free survival events for AAP & ADT (24%) compared to ADT (40%) at a median of 85 months follow-up.

[1] An update search was run on 26 July 2023 due to an identified issue with the MeSH indexing in the databases searched
[2] n=460 in James et al 2017; n=459 in Attard et al 2022. It is not clear why these numbers differ
[3] This median follow-up was for both metastatic and non-metastatic patients. Median follow-up was not separately reported for non-metastatic patients
[4] This median follow-up was for both metastatic and non-metastatic patients. Median follow-up was not separately reported for non-metastatic patients
[5] Defined as time from randomisation to death from any cause
[6] Defined as time from randomisation to death from any cause or to distant metastasis confirmed by imaging

- *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 (12%) and docetaxel & ADT (14%) at a median of 48 months follow-up.

- **Progression free survival[7] (critical outcome).**
  - *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 (8% vs 31%) and 85 months (26% vs 51%) follow-up. The same RCT also provided high certainty evidence of statistically significantly fewer progression free survival events for AAP & ADT (18%) compared to ADT (37%) 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 (9%) compared to docetaxel & ADT (24%) 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 (6%) and docetaxel & ADT (14%) at a median of 48 months follow-up.

- **Quality of life (important outcome).**
  - No evidence relating to quality of life was identified for AAP & ADT compared to ADT.
  - *For AAP & ADT vs docetaxel & ADT:* One RCT provided low certainty evidence of no statistically significant difference in global-quality of life[8] between AAP & ADT and docetaxel & ADT at two years follow-up. The difference between groups (3.0 points favouring AAP & ADT[9]) was less than the pre-defined criterion of >4.0 points for a clinically meaningful difference.

- **Symptom alleviation (important outcome).**
  - *For AAP & ADT vs ADT:* One RCT provided low certainty evidence of no statistically significant difference in symptomatic skeletal events[10] between AAP & ADT (2%) and ADT (4%) 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 (3%) and docetaxel & ADT (3%) at a median of 48 months follow-up.

- **Prostate cancer-specific survival[11] (important outcome).**
  - *For AAP & ADT vs ADT:* One RCT provided high certainty evidence of statistically significantly fewer prostate cancer-specific deaths for AAP & ADT (11%) compared to ADT (19%) 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 (4%) and docetaxel & ADT (5%) at a median of 48 months follow-up.

[7] This outcome was reported as failure-free survival (defined as time from randomisation to biochemical failure, local progression, distant metastasis or death from prostate cancer) and progression free survival (defined as time from randomisation to local progression, distant metastasis or death from prostate cancer (excluding biochemical failure))
[8] Assessed using the EORTC QLQ-C30 version 3, a self-reported questionnaire developed to assess quality of life in cancer patients. Questions from the global-quality of life scale were 'how would you rate your overall health during the last week' and 'how would you rate your overall quality of life during the last week'. Scores were standardised to a value between 0 and 100 with higher scores indicating better quality of life
[9] Individual group scores were only presented graphically
[10] Symptomatic skeletal events was not defined in any of the included STAMPEDE papers. However, it was described as a "more subjective" outcome in the trial protocol
[11] Defined as time from randomisation to death from prostate cancer

In terms of safety:

- **Adverse effects.**
  - *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[12] were experienced by 38% of AAP & ADT patients and 29% of ADT patients. The groups were not statistically compared. 13% of patients permanently stopped AAP due to excessive toxicity.
  - No evidence relating to safety was identified for AAP & ADT compared to docetaxel & ADT.

In terms of cost effectiveness:

- One analysis, using an NHS in England perspective and a lifetime time horizon, concluded that AAP & ADT is not cost effective compared to ADT using the 2017/2018 published price of abiraterone acetate (incremental cost effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained £149,748). The study 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.
- No evidence relating to cost effectiveness was identified for AAP & ADT compared to docetaxel & ADT.

In terms of 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.

Criteria used to define 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 two 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.

[12] Grade 3 = severe or medically significant but not immediately life threatening; Grade 4 = life-threatening consequences; Grade 5 = death related to adverse event

[13] In the paper by Sydes et al (2018), all the cut-off values for PSA concentration are described as greater than (>), rather than greater than or equal to (≥). In the paper by James et al (2017) the inclusion criteria for relapsing disease are described as <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

[14] These patients are included in the description of the inclusion criteria in the Attard et al abstract, but not in the full text

Patients were intended for long-term treatment with ADT that started no longer than 12 weeks before randomisation.

Dose of abiraterone and prednisolone used to treat high-risk, non-metastatic, hormone sensitive prostate cancer:

- In the STAMPEDE RCT, patients received abiraterone acetate (1,000mg) orally daily. Patients in the 111 UK study sites also received 5mg prednisolone daily. In the five Swiss study sites patients received 5mg of daily prednisone (rather than prednisolone). Patients also received ADT.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

Limitations reducing certainty in the outcomes reported in the STAMPEDE trial for the comparison of AAP plus ADT to ADT included lack of, or uncertainty about blinding for the subjective outcome of symptom alleviation and lack of statistical comparison between groups for safety outcomes. Limitations reducing certainty in the outcomes reported in the STAMPEDE trial for the comparison of AAP plus ADT to docetaxel plus ADT included uncertainty about the similarity of the groups at baseline and the completeness of follow-up, and uncertainty about assessor blinding and lack of patient blinding for the subjective outcomes of quality of life and symptom alleviation. For both comparisons, there was additional uncertainty about the precision of many outcomes due to wide confidence intervals.

Limitations introducing uncertainty to the cost effectiveness evidence include modelled lifetime estimates based on trial data at a median follow-up of three years and a lack of confidence intervals reported for the ICER. The analysis also used the 2017/2018 published cost for abiraterone acetate, due to the actual cost being redacted. This may not reflect the actual price of abiraterone acetate at the time or the present cost.

Conclusion:

This evidence review includes one multi-arm, multi-stage platform RCT (STAMPEDE). This provided data comparing AAP plus ADT to ADT for the critical outcomes of overall survival, metastasis-free survival and progression free survival. These reported a statistically significant advantage for AAP plus ADT for outcomes reported at a median of 85 months follow-up. For outcomes reported at a median of 40 months follow-up there was also a statistically significant advantage for failure-free survival (progression free survival including biochemical failure) but not for overall survival. There was also evidence for this comparison for the important outcomes of symptom alleviation and prostate cancer-specific survival. A statistically significant advantage was reported for AAP plus ADT for prostate cancer-specific survival at a median of 85 months, but not for symptom alleviation which was only reported at a median of 40 months.

The STAMPEDE trial also provided data comparing AAP plus ADT to docetaxel plus ADT. Generally, there were no statistically significant differences between groups at a median of 48 months follow-up for most of the critical or important outcomes, or at two years follow-up for the important outcome of quality of life. The exception was progression free survival, where a statistically significant advantage for AAP plus ADT was seen when biochemical failure was included in the outcome definition but not when this was excluded.

For safety outcomes, a higher proportion of AAP plus ADT patients compared to ADT patients reported serious adverse events. However, the groups were not statistically compared. No safety outcomes were separately reported for patients with non-metastatic disease for AAP plus ADT compared to docetaxel plus ADT. The relative safety of AAP plus ADT compared to current standard care is therefore uncertain.

The cost effectiveness evidence indicated that AAP plus ADT is not cost effective compared to ADT with an ICER per QALY of £149,748 using an NHS in England perspective, the 2017/2018 published cost of abiraterone acetate and a lifetime time horizon. No evidence relating to cost effectiveness was identified for AAP plus ADT compared to docetaxel plus ADT.

Patients with non-metastatic disease formed a subgroup within the STAMPEDE platform trial. No other subgroup analyses for non-metastatic patients were reported in the included papers.

The multi-arm, multi-stage platform RCT identified for this review therefore provided generally high to moderate certainty evidence favouring AAP plus ADT compared to ADT for clinical effectiveness outcomes at 85 months follow-up. There was generally low certainty evidence of no difference in clinical effectiveness outcomes between AAP plus ADT and docetaxel plus ADT at 48 months follow-up. The evidence relating to the relative safety of AAP plus ADT to standard care was uncertain. There was evidence that AAP plus ADT is not cost effective compared to ADT based on the 2017/2018 published price.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In high-risk, non-metastatic hormone sensitive prostate cancer, what is the clinical effectiveness of abiraterone acetate and prednisolone compared with current standard care?
2. In high-risk, non-metastatic hormone sensitive prostate cancer, what is the safety of abiraterone acetate and prednisolone compared with current standard care?
3. In high-risk, non-metastatic hormone sensitive prostate cancer, what is the cost effectiveness of abiraterone acetate and prednisolone compared with current standard care?
4. 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?
5. From the evidence selected, what are the criteria used by the research studies to define high-risk, non-metastatic hormone sensitive prostate cancer?
6. From the evidence selected, what dose of abiraterone acetate and prednisolone was used to treat high-risk, non-metastatic hormone sensitive prostate cancer?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 29th June 2023 and 26th July 2023[15].

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

[15] An update search was run on 26 July due to an identified issue with the MeSH indexing in the databases searched

4. Summary of included studies

One multi-arm, multi-stage platform RCT (STAMPEDE) (published in four papers) was identified for inclusion. Two of the STAMPEDE papers reported outcomes comparing AAP plus ADT to ADT at a median of 40 and 85 months follow-up in patients with high-risk, non-metastatic prostate cancer. The other two STAMPEDE papers reported a comparison of AAP plus ADT and docetaxel plus ADT at two years and at a median of 48 months follow-up in patients with high-risk, non-metastatic prostate cancer.

One cost effectiveness study was identified for inclusion. This compared the cost effectiveness of AAP plus ADT to ADT in patients with high-risk, non-metastatic prostate cancer using data from the STAMPEDE trial. No evidence relating to cost effectiveness was identified for AAP plus ADT compared to docetaxel plus ADT.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Clarke et al 2022 Cost effectiveness analysis using data from the STAMPEDE trial (see below)	1,011 patients with high-risk non-metastatic prostate cancer AAP & ADT: n=515 ADT: n=496 Outcomes were reported for a M0 subgroup which included patients who initially presented without metastasis and patients with only lymph node metastasis The authors refer to other STAMPEDE publications for fuller details of the population and inclusion and exclusion criteria (see below) Patients with non-metastatic disease formed a subgroup within this analysis. No other subgroup analysis reported for non-metastatic patients	**Intervention** Abiraterone acetate (1,000mg) orally daily and 5mg prednisolone[a] daily (AAP). Patients also received ADT **Comparison** ADT See below for details of concomitant treatment in STAMPEDE	**Important outcomes** • Cost effectiveness • ICER per QALY gained over lifetime time horizon
STAMPEDE (AAP & ADT vs ADT) (reported in Attard et al 2022 and James et al 2017) Multi-arm, multi-stage platform RCT	915 patients with high-risk non-metastatic prostate cancer AAP & ADT: n=460[b] ADT: n=455 Patients with newly diagnosed disease formed 95% of the AAP & ADT and 97% of the ADT groups respectively. Other	**Intervention** Abiraterone acetate (1,000mg) orally daily and 5mg prednisolone[a] daily (AAP). Patients also received ADT Patients received AAP for a median of 23.7 months **Comparison**	**Critical outcomes** • Overall survival[c] at median 40 and 85 months • Metastasis-free survival[d] events at median 85 months • Progression free survival • Failure-free survival[e] events at median 40 and 85 months

Study	Population	Intervention and comparison	Outcomes reported

Multi-centre (116 centres), 2 countries (UK and Switzerland)	patients had relapsing disease
	
	Patients were intended for long-term treatment with ADT that started no longer than 12 weeks before randomisation.
	
	The baseline characteristics were described as well balanced between groups
	
	Patients with non-metastatic disease formed a subgroup within this platform RCT. No other subgroup analysis reported for non-metastatic patients
		ADT
		
		Local radiotherapy was mandated, unless contraindicated, for node negative disease and encouraged for node positive disease. Local radiotherapy was received by 81% of AAP & ADT patients and 82% of ADT patients
			• Progression free survival[f] events at median 85 months
			
			Important outcomes
			• Symptom alleviation
			  • Symptomatic skeletal events[g] at median 40 months
			• Prostate cancer-specific survival[h] events at median 85 months
			• Safety
			  • Adverse events at 24 months
			  • Reasons for permanently stopping AAP at 24 months

STAMPEDE (AAP & ADT vs docetaxel & ADT) (reported in Rush et al 2022 and Sydes et al 2018)
 	
Multi-arm, multi-stage platform RCT
 	
Multi-centre (105 centres), 2 countries (UK and Switzerland)
	224 patients with high-risk non-metastatic prostate cancer
	
	AAP & ADT: n=150
	Docetaxel & ADT: n=74[i]
	
	Papers included both metastatic and non-metastatic patients. Baseline characteristics were not separately reported for non-metastatic patients. It is not clear if the baseline characteristics were similar between groups for non-metastatic patients
	
	Patients with non-metastatic disease formed a subgroup within this platform RCT. No other subgroup analysis reported for non-metastatic patients
		Intervention
		Abiraterone acetate (1,000mg) daily and 5mg prednisolone/prednisone[b] daily (AAP). Patients also received standard care with long term hormone therapy with luteinizing hormone-releasing hormone analogues (ADT) or orchidectomy[j]
		
		AAP duration was capped after 2 years in non-metastatic patients who were receiving radical radiotherapy
		
		Comparison
		Docetaxel chemotherapy (75mg/m^2 IV) administered 3 times a week for up to 6 cycles. Patients received 5mg prednisolone/prednisone twice daily. Patients also received standard care (described above)
		
		Local radiotherapy was mandated, unless contraindicated, for node negative disease and encouraged for node positive disease. Radiotherapy was planned for 79% AAP & ADT patients and 77% docetaxel & ADT patients
			Critical outcomes
			• Overall survival at median 48 months
			• Metastasis-free survival events at median 48 months
			• Progression free survival
			  • Failure-free survival events at median 48 months
			  • Progression free survival events at median 48 months
			
			Important outcomes
			• Quality of life
			  • Global quality of life[k] at 2 years
			• Symptom alleviation
			  • Symptomatic skeletal events at median 48 months
			• Prostate cancer-specific survival events at median 48 months

Study	Population	Intervention and comparison	Outcomes reported
Abbreviations AAP: Abiraterone acetate and prednisolone; ADT: Androgen deprivation therapy; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ICER: Incremental cost effectiveness ratio; IV: Intravenous; m: Metre; mg: Milligrams; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; UK: United Kingdom			
a Patients at the UK centres received prednisolone. However, it is stated that patients at the five Swiss centres received prednisone. In some papers, the intervention is described in the text as prednisolone, in others as prednisolone/prednisone b n=460 in James et al 2017; n=459 in Attard et al 2022. It is not clear why these numbers differ c Overall survival was defined as time from randomisation to death from any cause d Metastasis-free survival was defined as time from randomisation to death from any cause or to distant metastasis confirmed by imaging e Failure-free survival was defined as time from randomisation to biochemical failure, local progression, distant metastasis or death from prostate cancer f Progression free survival was defined as time from randomisation to local progression, distant metastasis or death from prostate cancer (excluding biochemical failure) g Symptomatic skeletal events was not defined in any of the included STAMPEDE papers. However, it was described as a “more subjective” outcome in the trial protocol h Prostate cancer-specific survival was defined as time from randomisation to death from prostate cancer i In Rush et al 2022, quality of life was reported for 137 AAP & ADT patients and 71 docetaxel & ADT patients j The details reported in the paper relate to both patients with metastatic and non-metastatic disease. It is not clear if any non-metastatic patients received orchidectomy k Quality of life was assessed using the EORTC QLQ-C30 version 3, a self-reported questionnaire developed to assess quality of life in cancer patients. Questions from the global-quality of life scale were ‘how would you rate your overall health during the last week’ and ‘how would you rate your overall quality of life during the last week’. Scores were standardised to a value between 0 and 100 with higher scores indicating better quality of life. The pre-defined criterion for a clinically meaningful difference in global-quality of life was >4.0 points			

5. Results

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[16] 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[17] and 85 months follow-up. This RCT also reported a comparison of AAP plus ADT to docetaxel plus ADT at median 48[18] 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	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.

[16] Defined as time from randomisation to death from any cause
[17] This median follow-up was for both metastatic and non-metastatic patients. Median follow-up was not separately reported for non-metastatic patients
[18] This median follow-up was for both metastatic and non-metastatic patients. Median follow-up was not separately reported for non-metastatic patients

Outcome	Evidence statement
Certainty of evidence: High to low	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[19] 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[20] and progression free survival[21]. **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)**

[19] Defined as time from randomisation to death from any cause or to distant metastasis confirmed by imaging
[20] Defined as time from randomisation to biochemical failure, local progression, distant metastasis or death from prostate cancer
[21] Defined as time from randomisation to local progression, distant metastasis or death from prostate cancer (excluding biochemical failure)

Outcome	Evidence statement
	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[22]. 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)[23]. Individual group scores were only presented graphically. **(LOW)**

[22] A self-reported questionnaire developed to assess quality of life in cancer patients. Questions from the global-quality of life scale were 'how would you rate your overall health during the last week' and 'how would you rate your overall quality of life during the last week'. Scores were standardised to a value between 0 and 100 with higher scores indicating better quality of life.
[23] The figures reported differ in different sections of the paper. These data were extracted from the paper supplement.

Outcome	Evidence statement
	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[24]. **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[25] 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*

[24] Symptomatic skeletal events was not defined in any of the included STAMPEDE papers. However, it was described as a "more subjective" outcome in the trial protocol

[25] Defined as time from randomisation to death from prostate cancer

Outcome	Evidence statement
	• 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[26] 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**)

[26] Defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0 or later version 4.0) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant but not immediately life threatening; Grade 4 = life-threatening consequences; Grade 5 = death related to adverse event

Outcome	Evidence statement
	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[27]. 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.

[27] The analysis used the 2017/2018 published cost for abiraterone acetate due to the actual cost being redacted. This may not reflect the actual price of abiraterone acetate at the time or the present cost

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[28] In some descriptions of the STAMPEDE population[29], 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	

[28] In the paper by Sydes et al (2018), all the cut-off values for PSA concentration are described as greater than (>), rather than greater than or equal to (≥). In the paper by James et al (2017) the inclusion criteria for relapsing disease are described as <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

[29] These patients are included in the description of the inclusion criteria in the Attard et al abstract, but not in the full text

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of AAP compared to current standard care for the treatment of high-risk, non-metastatic hormone sensitive prostate cancer. The critical outcomes of interest were overall survival, metastasis-free survival and progression free survival. Important outcomes were quality of life, symptom alleviation and prostate cancer-specific survival and safety outcomes.

Evidence was available from one multi-arm, multi-stage platform RCT (STAMPEDE), published in four papers. Two of the papers reported outcomes comparing AAP plus ADT to ADT at a median of 40 and 85 months follow-up. The two remaining papers reported a comparison of AAP plus ADT to docetaxel plus ADT at two years and a median of 40 months follow-up.

STAMPEDE was a multi-centre platform trial assessing different treatment regimens for both metastatic and non-metastatic patients. Patients were randomised to the treatments received. The comparison of AAP plus ADT to ADT was described as a "separate trial" done within the multi-arm, multistage platform protocol by Attard et al 2022. In an earlier paper, James et al 2017 stated that patients were randomly assigned in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate and prednisolone adding that patients were "assigned contemporaneously to ADT alone or with abiraterone and prednisolone". The authors state that this comparison of AAP plus ADT to ADT was "the first comparison incorporated after trial initiation". Sydes et al 2018 described their comparison of abiraterone acetate and docetaxel as a "pre-specified (but not pre-powered) analysis using only patients who were randomised during a period of the study when recruitment to the research arms overlapped." However, they also described the comparison as 'opportunistic' stating that the STAMPEDE trial "assessed both of these treatment approaches [AAP plus ADT and docetaxel plus ADT] separately against the previous SOC [standard of care]". Stratified randomisation allocated patients 2:1:2 to standard of care; standard of care and docetaxel and prednisolone; or standard of care and abiraterone acetate and prednisolone. The patients included in the analysis were contemporaneously randomised to AAP plus ADT or docetaxel plus ADT between 2011 and 2013.

The STAMPEDE trial also included treatment arms that are outside the scope of this evidence review. The subgroup analyses according to metastatic status were pre-specified.

The STAMPEDE trial was conducted at 116 centres[30] for the comparison of AAP plus ADT and ADT and 105 centres for the comparison of AAP plus ADT and docetaxel plus ADT. For both comparisons, five centres were in Switzerland with the remainder in the UK. The patients reported in the analyses included in this evidence review were recruited between 2011 and 2014.

The STAMPEDE trial had defined inclusion criteria for non-metastatic patients, although there were slight variations in the descriptions of these criteria between the different publications reporting results from the STAMPEDE trials. For example, whether cut-off levels were described as greater than (>) or greater than or equal to (≥). It was also unclear whether patients with nodal relapse were included within the definition of patients with relapsing disease with high risk features due to a lack of clarity about how the inclusion criteria were described within the papers.

[30] The figure of 113 centres is given in the paper by Attard et al 2022 whereas James et al states that there were 116 centres. It is not clear why the number of centres reported differs in the two papers

Attard et al 2022 was the only one of the four included papers that focused specifically on non-metastatic patients. This paper included baseline characteristics for non-metastatic patients reported separately for the treatment arms within scope of this evidence review and stated that the groups were similar at baseline. Other papers included both metastatic and non-metastatic patients with results for non-metastatic patients reported as subgroup analysis. Within these papers there was limited information specifically about the patients with non-metastatic disease and it was not always clear whether details reported about the population applied to the non-metastatic patients.

The majority (approximately 80%) of patients with non-metastatic disease receiving AAP plus ADT, ADT or docetaxel plus ADT also received radiotherapy.

The dosage of abiraterone acetate was consistently reported as 1,000 mg orally daily for STAMPEDE participants accompanied by 5mg prednisolone daily in the UK study sites or 5mg prednisone daily in the Swiss centres.

The maximum number of patients receiving each treatment was 460 and 455 for the comparison between AAP plus ADT and ADT, and 150 and 74 for the comparison between AAP plus ADT and docetaxel plus ADT respectively. The numbers of patients reported in the different papers differed slightly with the reason for this usually stated. However, it was not clear why the number of patients receiving AAP plus ADT differed in James et al and Attard at al (460 and 459 respectively). Power calculations were performed within the STAMPEDE platform trial. However, there was no pre-defined sample size for patients with non-metastatic disease and no specific sample size calculations for the comparisons and patients within scope of this evidence review. It is not clear if the analyses reported were sufficiently powered to detect differences between groups.

The follow-up period for the comparison between AAP plus ADT and ADT was of sufficient duration for the outcomes reported at a median of 85 months follow-up. Symptom alleviation was only reported at a median of 40 months which may not have been of sufficient duration to detect a difference as the number of events reported was low for both groups at less than 5%. Safety outcomes were reported at two years which reflects the duration of treatment with AAP. Outcomes comparing AAP plus ADT to docetaxel plus ADT were reported at a median of 48 months. Longer follow-up would be beneficial for the outcomes reported for this comparison for this non-metastatic patient population.

It was deemed impracticable to blind patients to study treatment in the STAMPEDE trial. This is unlikely to impact the objective outcomes reported, but does introduce a risk of bias for more subjective outcomes such as quality of life and symptom alleviation. It is not clear if outcome assessors were blinded to treatment assignment for more subjective outcomes, although it was specified that the determination that prostate cancer was the cause of death was assessed by clinicians without knowledge of patient's group.

Evidence comparing AAP plus ADT to ADT was identified for all three of the critical outcomes and two of the three important outcomes about clinical effectiveness. The remaining important outcome of quality of life was listed as a secondary outcome for the STAMPEDE trial in the paper by James et al 2017, with the "data not shown". No reason was given for why the quality of life data were not reported. Quality of life was not listed as an outcome in the later paper for this comparison by Attard et al 2022. For the comparison between AAP plus ADT and docetaxel plus ADT, evidence was identified for all three of the critical outcomes and all three of the important outcomes for clinical effectiveness.

Safety outcomes were separately reported for non-metastatic patients for the comparison between AAP plus ADT and ADT, with a higher proportion of patients experiencing serious

adverse events (≥Grade 3) with AAP plus ADT. However, the groups were not statistically compared. No safety outcomes were separately reported for AAP plus ADT compared to docetaxel plus ADT for patients with non-metastatic disease. The relative safety of AAP plus ADT compared to current standard care is therefore uncertain.

A minimal clinically important difference was reported by Rush et al 2022 for quality of life. No information about what any minimal clinically important thresholds or differences might be was reported for any of the other outcomes.

Limitations reducing certainty in the outcomes reported in the STAMPEDE trial for the comparison of AAP plus ADT to ADT included lack of, or uncertainty about blinding for the subjective outcome of symptom alleviation and lack of statistical comparison between groups for safety outcomes. Limitations reducing certainty in the outcomes reported in the STAMPEDE trial for the comparison of AAP plus ADT to docetaxel plus ADT included uncertainty about the similarity of the groups at baseline and the completeness of follow-up, and uncertainty about assessor blinding and lack of patient blinding for the subjective outcomes of quality of life and symptom alleviation. For both comparisons, there was additional uncertainty about the precision of many of the outcomes reported due to wide confidence intervals.

The cost effectiveness of AAP plus ADT compared to ADT was reported by one analysis based on the STAMPEDE data. This analysis used an English NHS perspective over a lifetime time horizon. Limitations introducing uncertainty to the cost effectiveness evidence include modelled lifetime estimates based on trial data at a median follow-up of only three years and the fact that confidence intervals were not reported around the ICER. The analysis also used the 2017/2018 published cost for abiraterone acetate as the actual cost was redacted which may not reflect the price of abiraterone acetate at the time of the analysis or the present cost.

The cost effectiveness analysis included both metastatic and non-metastatic patients. Subgroup analysis for patients described as non-metastatic was reported. However, the number of non-metastatic patients included in this analysis was higher than in other STAMPEDE papers. The non-metastatic patient subgroup was described as including patients who initially presented without metastasis and patients with only lymph node metastasis, which may account for the difference in patient numbers. Based on the patient numbers reported in the different STAMPEDE papers, patients with lymph node metastasis included in the cost effectiveness analysis are likely to have been less than 10% of the included patients.

Patients with non-metastatic disease formed a subgroup within the STAMPEDE platform trial. No other subgroup analyses for non-metastatic patients were reported in the included papers.

7. Conclusion

This evidence review includes one multi-arm, multi-stage platform RCT (STAMPEDE). This provided data comparing AAP plus ADT to ADT for the critical outcomes of overall survival, metastasis-free survival and progression free survival. These reported a statistically significant advantage for AAP plus ADT for outcomes reported at a median of 85 months follow-up. For outcomes reported at a median of 40 months follow-up there was also a statistically significant advantage for failure-free survival (progression free survival including biochemical failure) but not for overall survival. There was also evidence for this comparison for the important outcomes of symptom alleviation and prostate cancer-specific survival. These reported a statistically significant advantage for AAP plus ADT for prostate cancer-specific survival at a median of 85 months, but not for symptom alleviation which was only reported at a median of 40 months.

The STAMPEDE trial also reported a comparison of AAP plus ADT and docetaxel plus ADT. Generally, there were no statistically significant differences between groups at a median of 48 months follow-up for most of the critical or important outcomes, or at two years follow-up for the important outcome of quality of life. The exception was progression free survival, where a statistically significant advantage for AAP plus ADT was seen when biochemical failure was included in the outcome definition but not when this was excluded.

For safety outcomes, a higher proportion of AAP plus ADT patients compared to ADT patients reported serious adverse events. However, the groups were not statistically compared. No safety outcomes were separately reported for patients with non-metastatic disease for AAP plus ADT compared to docetaxel plus ADT. The relative safety of AAP plus ADT compared to current standard care is therefore uncertain.

The risk of bias for the comparison of AAP plus ADT to ADT was generally low, with limitations reducing the certainty in the outcomes including lack of blinding in relation to more subjective outcomes and the lack of statistical comparison for safety outcomes. There was more risk of bias for the comparison of AAP plus ADT to docetaxel plus ADT including uncertainty about the similarity of the groups at baseline, the completeness of follow-up and lack of blinding for the subjective outcomes. For both comparisons, there was additional uncertainty about the precision of many of the outcomes reported due to wide confidence intervals.

The cost effectiveness evidence indicated that AAP plus ADT is not cost effective compared to ADT with an ICER per QALY of £149,748 using an NHS in England perspective and a lifetime time horizon. Limitations introducing uncertainty to the cost effectiveness evidence include modelled lifetime estimates based on trial data at a median follow-up of three years and a lack of confidence intervals reported for the ICER. The analysis also used the 2017/2018 published cost for abiraterone acetate, due to the actual cost being redacted. This may not reflect the actual price of abiraterone acetate at the time or the present cost. No evidence relating to cost effectiveness was identified for AAP plus ADT compared to docetaxel plus ADT.

Patients with non-metastatic disease formed a subgroup within the STAMPEDE platform trial. No other subgroup analyses for non-metastatic patients were reported in the included papers.

The multi-arm, multi-stage platform RCT identified for this review therefore provided generally high to moderate certainty evidence favouring AAP plus ADT compared to ADT for clinical effectiveness outcomes at 85 months follow-up. There was generally low

certainty evidence of no difference in clinical effectiveness outcomes between AAP plus ADT and docetaxel plus ADT at 48 months follow-up. The evidence relating to the relative safety of APP plus ADT to standard care was uncertain. There was evidence that AAP plus ADT is not cost effective compared to ADT based on the 2017/2018 published price.

Appendix A PICO Document

The review questions for this evidence review are:

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

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

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

4. 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?

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

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

P-Population and Indication	All people with high-risk, hormone sensitive, non-metastatic prostate cancer. [Patients described as hormone-relapsed, or castrate resistant are not included in this cohort.] [Newly diagnosed high risk, non-metastatic prostate cancer would be classified as: • Non-metastatic (M0) **AND EITHER** • Pelvic node positive (N1) **OR** • at least of two of: ○ tumour stage T3 or T4 ○ Gleason score 8-10 ○ Prostate specific antigen (PSA) ≥ 40 nanograms/ml] [Both newly diagnosed prostate cancer and relapsing prostate cancer with high-risk features should be included.] [Relapsing with high-risk features could be defined as having an interval of ≥12 months without treatment and a PSA concentration ≥4 nanograms/ml with a doubling time of <6 months or a PSA concentration ≥20 nanograms/ml] Subgroups of interest: • Newly diagnosed vs relapsing high risk prostate cancer • People of Afro-Caribbean origin • People of lower socioeconomic status
I-Intervention	Abiraterone acetate and prednisolone [This is given alongside androgen deprivation therapy (ADT) +/- radiotherapy]

C-Comparator	Current standard care [This includes either: • ADT +/- radiotherapy **OR** ADT and docetaxel chemotherapy+/- radiotherapy]
O-Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. <u>*Critical to decision-making:*</u> • **Overall survival** *This outcome 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.* [Overall survival is conventionally thought of as the gold standard for assessing survival benefit of cancer drug treatments. To determine a clinically meaningful difference in overall survival a large study with longer follow up is required.] • **Metastasis-free survival** *This outcome 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.* [Definitions of metastasis-free survival could include, but are not limited to, time to death from any cause or time to distant metastasis confirmed by imaging. Metastasis free survival is often used as a surrogate for overall survival.] • **Progression free survival** *This outcome 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.* [This may also be presented as failure-free survival, e.g. defined as time from treatment initiation to biochemical failure, local progression, distant metastases, or death from prostate cancer, or progression free-survival defined as failure-free survival but excluding biochemical failure.] <u>*Important to decision-making:*</u> • **Quality of life** *This outcome 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.* [Examples of quality-of-life tools include but are not limited to QLQ-OV28 and QLQ-C30.]

	• **Symptom alleviation** *This outcome 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.* [Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms.] • **Prostate cancer-specific survival** *This outcome 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.* [Prostate cancer-specific survival is defined as the time from starting treatment to death from prostate cancer.] *Safety* *These 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.* *Cost effectiveness*
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials pre-prints and guidelines.
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2013 to 29 June 2023. An update search was also run on 26 July 2023 due to an identified issue with the MeSH indexing in the databases searched which had resulted in studies using the terminology ‘abiraterone’ rather than ‘abiraterone acetate’ not being detected by the original search.

Medline search strategy 29 June 2023:

1	Prostatic Neoplasms/
2	(prostat* adj2 (cancer? or carcinoma?)).ti,ab,kf.
3	1 or 2
4	Abiraterone Acetate/
5	(Abiraterone Acetate or zytiga or zaytiga or zaitiga or yonsa).ti,ab,kf.
6	4 or 5
7	exp Prednisolone/
8	(prednis* or Deltacortril or Deltastab or Dilacort or Pevant or methylpred*).ti,ab,kf.
9	7 or 8
10	3 and 6 and 9
11	(comment or editorial or letter or review).pt.
12	10 not 11
13	3 and 6
14	limit 13 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
15	12 or 14
16	limit 15 to english language
17	limit 16 to yr="2013 -Current"

Medline search strategy 26 July 2023:

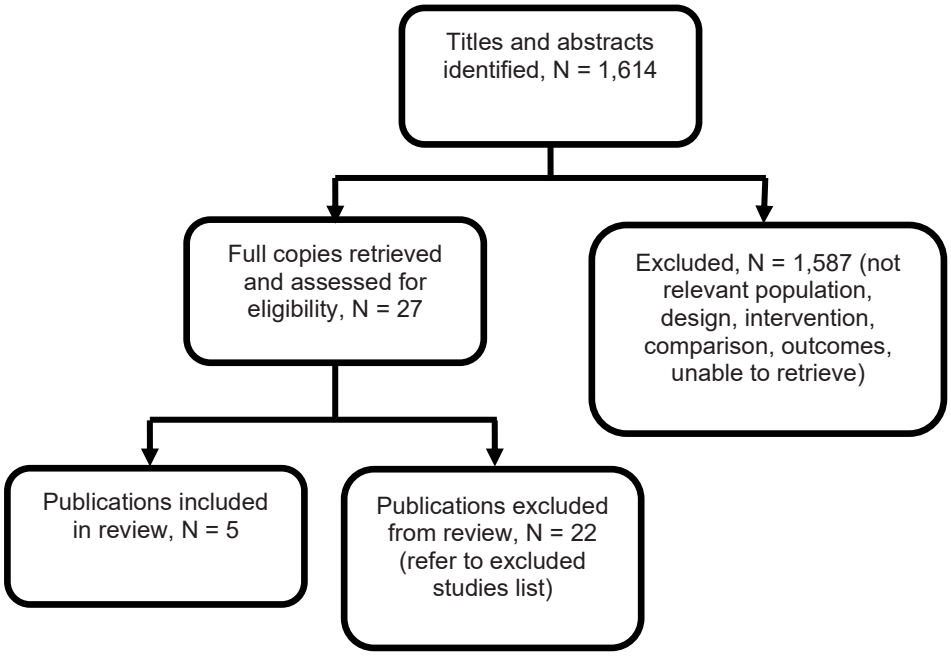
1	Prostatic Neoplasms/
2	(prostat* adj2 (cancer? or carcinoma?)).ti,ab,kf.
3	1 or 2
4	Abiraterone Acetate/
5	(Abiraterone or zytiga or zaytiga or zaitiga or yonsa).ti,ab,kf.
6	4 or 5
7	exp Prednisolone/
8	(prednis* or Deltacortril or Deltastab or Dilacort or Pevant or methylpred*).ti,ab,kf.
9	7 or 8

10	3 and 6 and 9
11	(comment or editorial or letter or review).pt.
12	10 not 11
13	3 and 6
14	limit 13 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
15	12 or 14
16	limit 15 to english language
17	limit 16 to yr="2013 -Current"

Appendix C Evidence selection

The literature search identified 1,614 potential references. These were screened using their titles and abstracts and 27 references potentially relating to the use of abiraterone and prednisolone for high-risk, non-metastatic hormone sensitive prostate cancer were obtained and assessed for relevance. Of these, five references are included in this evidence review. The 22 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399(10323):447-60.	Included in the review
James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. The New England journal of medicine. 2017;377(4):338-51.	Included in the review
No third reference supplied	N/A

Appendix D Excluded studies table

Study reference	Reason for exclusion
Autio KA, Antonarakis ES, Mayer TM, Shevrin DH, Stein MN, Vaishampayan UN, et al. Randomized Phase 2 Trial of Abiraterone Acetate Plus Prednisone, Degarelix, or the Combination in Men with Biochemically Recurrent Prostate Cancer After Radical Prostatectomy. European urology open science. 2021;34:70-8.	Population out of scope. Population do not meet the criteria specified for relapsing with high risk features
Branigan GL, Torrandell-Haro G, Soto M, Gelmann EP, Vitali F, Rodgers KE, et al. Androgen-targeting therapeutics mitigate the adverse effect of GnRH agonist on the risk of neurodegenerative disease in men treated for prostate cancer. Cancer medicine. 2022;11(13):2687-98.	Analysis not limited to the population or intervention of interest
De Nunzio C, Lombardo R, Tema G, Voglino O, Sica A, Baldassarri V, et al. Adverse events related to abiraterone and enzalutamide treatment: analysis of the EudraVigilance database and meta-analysis of registrational phase III studies. Prostate Cancer and Prostatic Diseases. 2020;23(2):199-206.	Population out of scope. Analysis focuses on patients with metastatic, castration resistant cancer
Efstathiou E, Davis JW, Pisters L, Li W, Wen S, McMullin RP, et al. Clinical and Biological Characterisation of Localised High-risk Prostate Cancer: Results of a Randomised Preoperative Study of a Luteinising Hormone-releasing Hormone Agonist with or Without Abiraterone Acetate plus Prednisone. European urology. 2019;76(4):418-24.	Population out of scope. Population do not meet the criteria specified for high risk
Hall ME, Padgett WJ, Klaassen Z, Magee DE, Luckenbaugh AN, Laviana AA, et al. Association between RCT methodology and disease indication with mineralocorticoid-related toxicity for patients receiving abiraterone acetate for advanced prostate cancer: A meta-analysis of RCTs. Clinical genitourinary cancer. 2023.	Population out of scope. All but one of the included studies was on patients with metastatic cancer. The exception, James et al 2017, is already included in this evidence review
Huang S-W, Chen L-C, Tseng C-S, Chen C-H, Yuan L-H, Shau W-Y, et al. Risk of cognitive impairment in men with advanced prostate cancer treated with NHAs: A systematic review and network meta-analysis. Clinical and translational science. 2023;16(2):313-25.	Population out of scope. Patients described as castrate resistant
Kassem L, Shohdy KS, Abdel-Rahman O. Abiraterone acetate/androgen deprivation therapy combination versus docetaxel/androgen deprivation therapy combination in advanced hormone-sensitive prostate cancer: a network meta-analysis on safety and efficacy. Current medical research and opinion. 2018;34(5):903-10.	Population out of scope. Analysis focuses on patients with metastatic cancer
Koontz BF, Hoffman KE, Halabi S, Healy P, Anand M, George DJ, et al. Combination of Radiation Therapy and Short-Term Androgen Blockade With Abiraterone Acetate Plus Prednisone for Men With High- and Intermediate-Risk Localized Prostate Cancer. International journal of radiation oncology, biology, physics. 2021;109(5):1271-8.	Population out of scope. Population do not meet the criteria specified for high risk
McKay RR, Xie W, Ye H, Fennessy FM, Zhang Z, Lis R, et al. Results of a Randomized Phase II Trial of Intense Androgen Deprivation Therapy prior to Radical Prostatectomy in Men with High-Risk Localized Prostate Cancer. The Journal of urology. 2021;206(1):80-7.	Study is not assessing the effectiveness of abiraterone
Maluf FC, Schutz FA, Cronemberger EH, Luz MdA, Martins SPS, Muniz DQB, et al. A phase 2 randomized clinical trial of abiraterone plus ADT, apalutamide, or abiraterone and apalutamide in patients with advanced prostate cancer with non-castrate testosterone levels (LACOG 0415). European journal of cancer (Oxford, England : 1990). 2021;158:63-71.	Analysis not limited to the population or intervention of interest
Myint ZW, Momo HD, Otto DE, Yan D, Wang P, Kolesar JM. Evaluation of Fall and Fracture Risk Among Men With Prostate Cancer Treated With Androgen Receptor Inhibitors: A	Intervention out of scope. Study does not include any results for abiraterone

Systematic Review and Meta-analysis. JAMA network open. 2020;3(11):e2025826.	
Ong TA, Saad M, Lim J, Lee HH. Novel hormonal therapies in the management of advanced prostate cancer: extrapolating Asian findings to Southeast Asia. BMC Urology. 2023;23(1):4.	Population out of scope. Patients receiving abiraterone had metastatic disease
Santoni M, Guerra F, Conti A, Lucarelli A, Rinaldi S, Belvederesi L, et al. Incidence and risk of cardiotoxicity in cancer patients treated with targeted therapies. Cancer Treatment Reviews. 2017;59:123-31.	Analysis not limited to the population or intervention of interest
Spetsieris N, Boukovala M, Alafis I, Davis J, Zurita A, Wang X, et al. Abiraterone acetate plus prednisone in non-metastatic biochemically recurrent castration-naive prostate cancer. European journal of cancer (Oxford, England : 1990). 2021;157:259-67.	Population out of scope. Population do not meet the criteria specified for relapsing with high risk features
Sun G, Zhang X, Chen J, Liao B, Liu Z, Zhao J, et al. What kind of patients with castration-naive prostate cancer can benefit from upfront docetaxel and abiraterone: A systematic review and a network meta-analysis. Urologic oncology. 2018;36(12):505-17.	The analysis includes papers that do not meet the PICO criteria. The in scope data is from STAMPEDE. Limited information is provided and this analysis for these comparators has already been included directly from STAMPEDE papers. No additional outcomes reported in this analysis
Supiot S, Campion L, Pommier P, Dore M, Palpacuer C, Racadot S, et al. Combined abiraterone acetate plus prednisone, salvage prostate bed radiotherapy and LH-RH agonists (CARLHA-GEP12) in biochemically-relapsing prostate cancer patients following prostatectomy: A phase I study of the GETUG/GEP. Oncotarget. 2018;9(31):22147-57.	Population out of scope. Population do not meet the criteria specified for relapsing with high risk features
Rajwa P, Pradere B, Gandaglia G, van den Bergh RCN, Tsaur I, Shim SR, et al. Intensification of Systemic Therapy in Addition to Definitive Local Treatment in Nonmetastatic Unfavourable Prostate Cancer: A Systematic Review and Meta-analysis. European Urology. 2022;82(1):82-96.	The analysis includes papers that do not meet the PICO criteria. The in scope data is from STAMPEDE. Limited information is provided and this analysis for these comparators has already been included directly from STAMPEDE papers. No additional outcomes reported in this analysis
Roviello G, Corona SP, Generali D. Low dose versus standard dose of corticosteroids in the management of adverse events of special interest from abiraterone acetate: data from a literature-based meta-analysis. Medical oncology (Northwood, London, England). 2017;34(10):166.	Population out of scope. Patients described as castrate resistant
Wallis CJD, Klaassen Z, Bhindi B, Goldberg H, Chandrasekar T, Farrell AM, et al. Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naive Prostate Cancer: A Systematic Review and Network Meta-analysis. European urology. 2018;73(6):834-44.	This reports overall survival using STAMPEDE data in a subgroup analysis of patients without metastasis. Limited information is provided and this analysis for these comparators has already been included directly from STAMPEDE papers
Werutsky G, Maluf FC, Cronemberger EH, Carrera Souza V, Dos Santos Martins SP, Peixoto F, et al. The LACOG-0415 phase II trial: abiraterone acetate and ADT versus apalutamide versus abiraterone acetate and apalutamide in patients with advanced prostate cancer with non-castration testosterone levels. BMC cancer. 2019;19(1):487.	Trial protocol
Zhu X, Wu S. Risk of hypertension in cancer patients treated with abiraterone: a meta-analysis. Clinical hypertension. 2019;25:12.	Population out of scope. Analysis focuses on patients with metastatic cancer
Zhuang J, Wang Y, Fu Y, Huang H, Lyu X, Zhang S, et al. Androgen deprivation therapy plus abiraterone or docetaxel as neoadjuvant therapy for very-high-risk prostate cancer: a pooled analysis of two phase II trials. Frontiers in Pharmacology. 2023;14:1217303.	Interventions were received as treatment prior to surgery. Outcomes reported after surgery

Appendix E Evidence Table

For abbreviations see list after table. For the JBI checklist for RCTs see Appendix F.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399(10323):447-60 **Study location** Multi-centre (113 centres), 2 countries (UK and Switzerland) **Study type** Analysis of data from the STAMPEDE RCT **Study aim**	Patients with high-risk non-metastatic prostate cancer **Inclusion criteria** Patients with high-risk disease 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	**Intervention** Abiraterone acetate (1,000mg) orally daily and 5mg prednisolone[33] daily (AAP). Patients also received ADT Patients received AAP for a median of 23.7 months (IQR 17.6 to 24.1) **Comparison** ADT Patients could receive ADT for 3 years and could also receive surgery and luteinising-hormone-releasing hormone antagonists that started no longer than 12 weeks before randomisation Local radiotherapy was mandated, unless contraindicated, for node	Median follow-up: 85 months (interquartile range (IQR) 83 to 96) **Critical outcomes** **Overall survival[34]** *Number of deaths* • AAP & ADT: 95/459 (20.7%) • ADT: 142/455 (31.2%) HR 0.63 (95%CI 0.48 to 0.82) (p=0.0005) **Metastasis-free survival[35]** *Number of metastasis-free survival events* • AAP & ADT: 111/459 (24.2%) • ADT: 183/455 (40.2%) HR 0.54 (95%CI 0.43 to 0.68) (p <0.0001) The 111 events in the APT & ADT group were death (n=60) and metastasis (n=51). The 183 events in the ADT group were death (n=73) and metastasis (n=110) **Progression free survival** *Number of failure-free survival[36] events* • AAP & ADT: 120/459 (26.1%)	This study was appraised using the JBI checklist for RCTs: 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Unclear 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments** STAMPEDE (Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) was a multi-arm, multi-stage platform trial assessing different treatment regimens

[33] The intervention is described as prednisolone. However, it is also stated that patients at the five Swiss centres received prednisone
[34] Defined as time from randomisation to death from any cause
[35] Defined as time from randomisation to death from any cause or to distant metastasis confirmed by imaging
[36] Defined as time from randomisation to biochemical failure, local progression, distant metastasis or death from prostate cancer

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
To investigate the efficacy of adding abiraterone acetate and prednisolone to ADT in patients with high-risk non-metastatic prostate cancer **Study dates** Recruitment 2011 to 2014	interval of ≥12 months without treatment and PSA ≥4ng/mL with a doubling time of <6 months, or PSA concentration ≥20ng/mL[31] In some descriptions of the STAMPEDE population[32], patients with nodal relapse were also listed in the inclusion criteria Patients were intended for long-term treatment with ADT that started no longer than 12 weeks before randomisation **Exclusion criteria** Patients with confirmed clinically significant cardiovascular disease e.g. severe angina, recent myocardial	negative disease and encouraged for node positive disease. Local radiotherapy was received by 81% of AAP & ADT patients and 82% of ADT patients	• ADT: 227/455 (51.0%) HR 0.39 (95%CI 0.31 to 0.49) (p not reported) *Number of progression free survival[37] events* • AAP & ADT: 84/459 (18.3%) • ADT: 166/455 (36.5%) HR 0.43 (95%CI 0.33 to 0.56) (p not reported) **Important outcomes** **Prostate cancer-specific survival[38]** *Number of prostate cancer-specific deaths* • AAP & ADT: 48/459 (10.5%) • ADT: 86/455 (18.9%) HR 0.52 (95%CI 0.36 to 0.75) (p not reported) **Safety** Safety outcomes reported at 24 months follow-up. No statistical comparison between groups reported for safety outcomes *Adverse events ≥ Grade 3[39]*	for both metastatic and non-metastatic patients The comparison of AAP & ADT to ADT was described as a "separate trial" done within the multi-arm, multistage platform protocol This pre-specified analysis focused specifically on the subgroup of patients with non-metastatic disease. However, some of the reported analyses included patients who received an additional drug (enzalutamide) which is outside the scope of this evidence review. Only results separately reported for patients receiving the intervention or comparator specified in the PICO are extracted Patients were randomly assigned to standard care (ADT) or combination therapy (AAP & ADT). Randomisation

[31] In some STAMPEDE papers the cut off levels are described as greater or less than (><), rather than greater/less than or equal to (≥≤)
[32] These patients are included in the description of the inclusion criteria in the Attard et al abstract, but not in the full text
[37] Defined as time from randomisation to local progression, distant metastasis or death from prostate cancer (excluding biochemical failure)
[38] Defined as time from randomisation to death from prostate cancer
[39] Defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0 or later version 4.0) where Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant but not immediately life threatening; Grade 4 = life-threatening consequences; Grade 5 = death related to adverse event

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	infarction or a history of cardiac failure **Total sample size** n=914 patients with non-metastatic disease AAP & ADT: n=459 ADT: n=455 **Baseline characteristics** *AAP & ADT* • Median age (years): 68 (range 44 to 84) • Newly diagnosed disease: 95% • Node positive: 42% • T3 or T4: 92% • Gleason 8 to 10: 77% • Median PSA (ng/mL): 34 (IQR 15 to 68) *ADT* • Median age (years): 67 (range 48 to 83) • Newly diagnosed disease: 97% • Node positive: 42% • T3 or T4: 90% • Gleason 8 to 10: 76%		• AAP & ADT: 169/451 (37.5%) • ADT: 130/455 (28.6%) *Grade 5 adverse events* Grade 5 adverse events in the AAP & ADT group were rectal adenocarcinoma (n=1), pulmonary haemorrhage (n=1) and a respiratory disorder (n=1). There were no Grade 5 adverse events in the ADT group *Grade 4 adverse events* Grade 4 adverse events in the AAP & ADT group were ALT increased (n=2), hypokalaemia (n=1) and anaemia (n=1). Grade 4 adverse events in the ADT group were anaemia (n=2) *Grade 3 adverse events* 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%) *Grade 1-2 adverse events* 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	was performed centrally using a computerised algorithm. Power calculations were performed for comparisons within the STAMPEDE platform. However, there was no pre-defined sample size for patients with non-metastatic disease. No sample size calculation was performed that was specific to the comparison and patients within scope of this evidence review Patients and clinicians were not blinded to study treatment as this was considered impracticable. This is unlikely to impact the objective outcomes reported. It is stated that death from prostate cancer was assessed by clinicians without knowledge of randomised groups. It is unclear whether other outcome assessors were blinded to treatment assignment Clinical effectiveness outcomes were assessed as intention-to-treat (n=914). Safety outcomes were assessed in patients who received AAP & ADT (n=451) or ADT (n=455). The groups

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Median PSA (ng/mL): 40 (IQR 16 to 83) The baseline characteristics were described as well balanced between the randomised groups by the authors		dysfunction (46%), anaemia (31%), insomnia (28%) and constipation (23%) *Reasons for permanently stopping AAP (n=451)* • Treatment complete: 266 (59%) • Excessive toxicity: 60 (13%) • Treatment refusal: 14 (3%) • Disease progression: 18 (4%) • Patient choice: 5 (1%) • Death: 3 (1%) • Clinician decision: 3 (1%) • Intercurrent illness: 1 (<1%) • Not stopped: 18 (4%) • Other (not further defined): 63 (14%) No details of the patients stopping AAP for different reasons provided	were not statistically compared for safety outcomes The authors stated that 238 patients in the AAP & ADT group and 230 in the ADT group had data available in the past year. 20 patients (4.4%) in the AAP & ADT group and 8 patients (1.8%) in the ADT group withdrew from the study The majority of patients had newly diagnosed disease. No information on patient ethnicity or socioeconomic status was reported. No subgroup analyses were reported The proportion of the 113 study sites that were UK centres was not reported in this paper. However, elsewhere it was reported that 111 of 116 STAMPEDE sites were in the UK (see James et al 2017). It is not clear why this analysis states 113 centres rather than the 116 STAMPEDE centres cited for this comparison in James et al **Source of funding:** See James et al 2017 for details of STAMPEDE funding

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

Clarke CS, Hunter RM, Gabrio A, Brawley CD, Ingleby FC, Dearnaley DP, et al. Cost-utility analysis of adding abiraterone acetate plus prednisone/prednisolone to long-term hormone therapy in newly diagnosed advanced prostate cancer in England: Lifetime decision model based on STAMPEDE trial data. PloS one. 2022;17(6):e0269192
 	
Study location
UK perspective
 	
Study type
Cost effectiveness study using data from the STAMPEDE RCT
 	
Study aim
To determine the value for money to the English NHS of adding AAP to standard care in men initiating long-
	Patients with high-risk non-metastatic prostate cancer
	
	Inclusion criteria
	Newly diagnosed and metastatic, node-positive, or high-risk locally advanced, non-metastatic prostate cancer, or disease previously treated with radical surgery or radiotherapy which was relapsing with certain high-risk features
	
	Exclusion criteria
	Patients with known severe cardiovascular disease
	
	The authors refer to other STAMPEDE publications for fuller details of the inclusion and exclusion criteria. See Attard et al 2022 for further details of STAMPEDE inclusion
		Intervention
		Abiraterone acetate (1,000mg) orally daily and 5mg prednisolone[41] daily (AAP). Patients also received ADT
		
		Comparison
		ADT[42]
		
		Non-metastatic patients in both treatment arms received AAP for 2 years
			Important outcomes
			
			Cost effectiveness
			
			ICER per QALY gained: £149,748
			• Lifetime costs
			  • AAP & ADT: £97,558
			  • ADT: £48,736
			  Difference: £48,821
			• Lifetime QALYs
			  • AAP & ADT: 7.03
			  • ADT: 6.70
			  Difference: 0.33
			
			Probability of AAP & ADT being cost effective compared to ADT at a threshold of £30,000/QALY: 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
				Appraisal with a checklist is not required for cost effectiveness studies
				
				Other comments
				Data for this cost utility analysis was taken from STAMPEDE, a multi-arm, multi-stage platform trial assessing different treatment regimens for both metastatic and non-metastatic patients conducted primarily in the UK
				
				Patients were recruited between 2011 and 2014 and data were included up to February 2017. Non-metastatic patients were followed-up for a median of 3.08 years
				
				The analysis used a Markov model with a lifetime (45 year) time horizon. The authors stated that the mean age in the youngest category of patients included in the analysis was 55 years
				
				Healthcare resource use costs were calculated using an

[41] The intervention is described as prednisolone/prednisone. It is stated that patients at the five Swiss centres received prednisone
[42] The authors state that changes were made to standard care during the course of the study, meaning that some patients in the ADT arm also received AAP, mostly during later disease stages. The number of ADT patients who also received AAP is not stated and it is not clear if this applied to any non-metastatic patients

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
term ADT for prostate cancer **Study dates** RCT recruitment 2011 to 2014 Costs were calculated using 2017-2018 prices	and exclusion criteria for non-metastatic patients Outcomes were reported for a M0 subgroup which included patients who initially presented without metastasis and patients with only lymph node metastasis **Total sample size** n=1,011 patients with non-metastatic disease AAP & ADT: n=515 ADT: n=496[40] The authors refer to other STAMPEDE publications for details of the population See Attard et al 2022 for further details of non-metastatic patients included in STAMPEDE			English NHS perspective at 2017-2018 prices. Cost information from trial data included investigational medications, other specific expensive medications (docetaxel, enzalutamide, cabazitaxel and radium) and general disease management costs (other medications, procedures, unscheduled visits, radiotherapy). A flat cost for serious adverse events was calculated using trial data. Published costs for end-of-life care for prostate cancer and costs for standard monitoring activities and stoppage of medication, where this implied additional healthcare resources, were also included The base-case cost for abiraterone was taken from the published British National Formulary NHS reference costs 2017-2018 (£97.68/ day). However, the authors stated that NHS purchases abiraterone acetate at an undisclosed discount. Sensitivity analysis explored the impact of using a lower price for abiraterone acetate

[40] Figures reported in a supplementary appendix. It is not clear why the number of patients is higher than in Attard et al 2022

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				Future costs were discounted at 3.5% per year Quality of life was assessed using the EORTC QLQ-C30 version 3[43]. Partially completed questionnaires were counted as 'missing' Results should be treated with caution due to uncertainties around modelled lifetime estimates based on trial data with a median 3 years follow-up. Confidence intervals were not reported for the ICER estimates **Source of funding:** The cost effectiveness analysis was supported by Cancer Research UK. See James et al 2017 for details of STAMPEDE funding
James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. The	Patients with high-risk locally advanced non-metastatic prostate cancer **Inclusion criteria**	Patients received AAP & ADT or ADT. See Attard et al 2022 for further details Patients with non-metastatic disease	Median follow-up: 40 months (range not reported). Median follow-up not separately reported for non-metastatic patients See Attard et al 2022 for outcome definitions unless otherwise stated	This study was appraised using the JBI checklist for RCTs. Questions relating to the design, conduct and analysis of the STAMPEDE trial are assessed in Attard et al 2022

[43] The EORTC QLQ-C30 is a self-reported questionnaire developed to assess quality of life in cancer patients. Questions from the global-quality of life scale were 'how would you rate your overall health during the last week' and 'how would you rate your overall quality of life during the last week'. Scores were standardised to a value between 0 and 100. Higher scores indicate better quality of life

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
New England journal of medicine. 2017;377(4):338-51 **Study location** Multi-centre (116 centres), 2 countries (UK and Switzerland) **Study type** Analysis of data from the STAMPEDE RCT **Study aim** To evaluate whether the earlier use of abiraterone in men who are initiating long-term ADT improves survival **Study dates** Recruitment 2011 to 2014	See Attard et al 2022 for STAMPEDE inclusion criteria[44] **Exclusion criteria** See Attard et al 2022 for STAMPEDE exclusion criteria **Total sample size** n=915 patients with non-metastatic disease AAP & ADT: n=460[45] ADT: n=455 Patient baseline characteristics were not separately reported for metastatic and non-metastatic patients See Attard et al 2022 for the baseline characteristics of non-metastatic patients who received AAP & ADT or ADT in STAMPEDE	received AAP for up to 2 years	**Critical outcomes** **Overall survival** *Number of deaths* • AAP & ADT: 34/460 (7.4%) • ADT: 44/455 (9.7%) HR 0.75 (95%CI 0.48 to 1.18) (p not reported) **Progression free survival** *Number of failure-free survival[46] events* • AAP & ADT: 38/460 (8.3%) • ADT: 142/455 (31.2%) HR 0.21 (95%CI 0.15 to 0.31) (p not reported) **Important outcomes** **Symptom alleviation** *Number of symptomatic skeletal[47] events* AAP & ADT: 11/460 (2.4%) • ADT: 19/455 (4.2%) HR 0.56 (95%CI 0.27 to 1.18) (p not reported)	**Other comments** STAMPEDE (Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) was a multi-arm, multi-stage platform trial assessing different treatment regimens for both metastatic and non-metastatic patients Patients were randomly assigned in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate and prednisolone. Patients were "assigned contemporaneously to ADT alone or with abiraterone and prednisolone". The authors state that this was "the first comparison incorporated after trial initiation" Many of the results reported were for a combined population of patients with metastatic and non-metastatic

[44] In James et al (2017) the inclusion criteria for relapsing disease are described as <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
[45] This figure was 459 in the paper by Attard et al 2022. It is not clear why this number differs
[46] Defined as time to the first of the following forms of treatment failure: biochemical (prostate-specific antigen) failure, progression of local, lymph-node, or distant metastasis or death from prostate cancer
[47] This outcome was not defined by James et al 2017 nor in other included STAMPEDE papers

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				disease. Patients with metastatic disease formed 52% of the population. Only outcomes with separate reporting for patients non-metastatic patients have been extracted Limited information was provided in this paper that was specifically about patients with non-metastatic disease. However, details about non-metastatic patients in the STAMPEDE trial for this comparison were reported in Attard et al 2022 The subgroup analysis according to metastatic status was pre-specified. No other subgroup analyses for non-metastatic patients were reported The authors stated that the overall survival results in patients with non-metastatic disease were immature No definition was provided for the outcome of symptomatic skeletal events in James et al. However, this was described as a “more subjective” outcome in the trial protocol

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				provided as a supplementary appendix to Attard et al 2022. Attard et al described skeletal related events as bone pain requiring radiotherapy and/or surgery, pathological fracture with or without disease progression at that cancer site and metastatic spinal cord compression. It is not clear if this relates to the outcome described as symptomatic skeletal events in James et al The authors stated that 111 of the 116 study sites were in the UK with the remaining 5 sites in Switzerland **Source of funding:** The STAMPEDE trial is sponsored by the UK Medical Research Council. Funding support was received from Cancer Research UK, the Medical Research Council, Janssen, Astellas Pharma, Clovis Oncology, Novartis, Pfizer and Sanofi-Aventis
Rush HL, Murphy L, Morgans AK, Clarke NW, Cook AD, Attard G, et al. Quality of Life in Men With Prostate Cancer Randomly Allocated to Receive Docetaxel or	Patients with high-risk locally advanced non-metastatic hormone sensitive prostate cancer **Inclusion criteria**	Patients received AAP & ADT or docetaxel & ADT. See Sydes et al 2018 for further details	Quality of life reported at 2 year follow-up **Important outcomes** **Quality of life**	This study was appraised using the JBI checklist for RCTs. Questions relating to the design, outcomes and analysis of the STAMPEDE trial are assessed in Attard et al 2022. Questions where the

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Abiraterone in the STAMPEDE Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2022;40(8):825-36 **Study location** Multi-centre (105 centres), 2 countries (UK and Switzerland) **Study type** Analysis of data from the STAMPEDE RCT **Study aim** To compare patient-reported quality of life for patients receiving abiraterone acetate and prednisolone/prednisone or docetaxel chemotherapy and prednisolone **Study dates** Recruitment 2011 to 2013	See Attard et al 2022 for STAMPEDE inclusion criteria **Exclusion criteria** See Attard et al 2022 for STAMPEDE exclusion criteria Patients had completed at least one quality of life questionnaire at any timepoint **Total sample size** n=208 patients with non-metastatic disease AAP & ADT: n=137 Docetaxel & ADT: n=71 Patient characteristics were not separately reported for metastatic and non-metastatic patients. It is not clear if the baseline characteristics were similar between groups for non-metastatic patients	Patients with non-metastatic disease received AAP for 2 years The proportion of patients receiving radiotherapy was not reported for non-metastatic patients	*Global-quality of life at 2 years assessed using the EORTC QLQ-C30 version 3*[48] No statistically significant difference between groups (difference 3.0 points (favouring AAP & ADT), 95%CI -2.4 to 8.3, p=0.275)[49] Individual group scores only presented graphically	response to Attard et al 2022 is relevant to and the same as for this paper are indicated by * below. Other questions show the responses relevant to the different comparator reported in this paper 1. Yes* 2. Yes* 3. Unclear 4. No* 5. No* 6. Unclear* 7. Yes 8. Unclear 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes* **Other comments** STAMPEDE (Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) was a multi-arm, multi-stage platform trial assessing different treatment regimens

[48] The EORTC QLQ-C30 is a self-reported questionnaire developed to assess quality of life in cancer patients. Questions from the global-quality of life scale were 'how would you rate your overall health during the last week' and 'how would you rate your overall quality of life during the last week'. Scores were standardised to a value between 0 and 100. Higher scores indicate better quality of life. The pre-defined criterion for a clinically meaningful difference in global-quality of life was >4.0 points

[49] The figures reported differ in different sections of the paper. These data were extracted from the paper supplement

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Information provided by the authors suggests that the non-metastatic population included both newly diagnosed and previously treated relapsing patients			for both metastatic and non-metastatic patients The patients included in this analysis were contemporaneously randomised to AAP & ADT or docetaxel & ADT between 2011 and 2013. The authors stated that there was no dedicated sample size calculation for the quality of life analysis Limited information was provided specifically about the non-metastatic patients. It is not clear if the 2 groups were similar at baseline Most outcomes reported in this paper were for a combined population of patients with metastatic or non-metastatic disease and are therefore out of scope for this evidence review. Global quality of life at 2 years was the only outcome separately reported for patients with non-metastatic disease Quality-of life outcomes were self-reported The STAMPEDE trial did not collect reasons for missing

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				questionnaires or impute missing data. The proportion of missing data at each time point was not separately reported for patients with non-metastatic cancer The number of study sites is not reported in this paper. However, in Sydes et al 2018, which reported the same comparison, data were collected from 100 of the 111 participating sites in the UK and 5 sites in Switzerland **Source of funding:** See James et al 2017 for details of STAMPEDE funding
Sydes MR, Spears MR, Mason MD, Clarke NW, Dearnaley DP, de Bono JS, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Annals of oncology : official journal of the European Society	Patients with high-risk non-metastatic prostate cancer **Inclusion criteria** See Attard et al 2022 for STAMPEDE inclusion criteria[50] **Exclusion criteria** See Attard et al 2022 for STAMPEDE exclusion criteria	**Intervention** Abiraterone acetate (1,000mg) daily and 5mg prednisolone/prednisone[51] daily (AAP). Patients also received standard care (see below) AAP duration was capped after 2 years in non-metastatic patients who were receiving radical radiotherapy	Median follow-up: 48 months (range not reported). Median follow-up not separately reported for non-metastatic patients See Attard et al 2022 for outcome definitions unless otherwise stated **Critical outcomes** **Overall survival** *Number of deaths* • AAP & ADT: 16/150 (10.7%) • Docetaxel & ADT: 6/74 (8.1%) HR 1.51 (95%CI 0.58 to 3.93) (p=0.395)	This study was appraised using the JBI checklist for RCTs. Questions relating to the design, outcomes and analysis of the STAMPEDE trial are assessed in Attard et al 2022. Questions where the response to Attard et al 2022 is relevant to and the same as for this paper are indicated by * below. Other questions show the responses relevant to the different comparator reported in this paper

[50] In Sydes et al (2018), all the cut-off values for PSA concentration are described as greater than (>), rather than greater than or equal to (≥)
[51] The intervention is described as prednisolone/prednisone. Other STAMPEDE publications state that patients at the five Swiss centres received prednisone

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
for Medical Oncology. 2018;29(5):1235-48 **Study location** Multi-centre (105 centres), 2 countries (UK and Switzerland) **Study type** Analysis of data from the STAMPEDE RCT **Study aim** To compare the efficacy of adding abiraterone or docetaxel to ADT and prednisolone in patients with high-risk prostate cancer **Study dates** Recruitment 2011 to 2013	**Total sample size** n=224 patients with non-metastatic disease AAP & ADT: n=150 Docetaxel & ADT: n=74 Most patient characteristics were not separately reported for metastatic and non-metastatic patients. It is not clear if the baseline characteristics were similar between groups for non-metastatic patients Node positive disease: AAP & ADT: 66/150 (44%) Docetaxel & ADT: 31/74 (42%)	**Comparison** Docetaxel chemotherapy (75mg/m2 IV) administered 3 times a week for up to 6 cycles. Patients received 5mg prednisolone/prednisone twice daily. Patients also received standard care (see below) Standard care was described as long-term ADT or, for most non-metastatic cases, ADT for ≥2 years and radiotherapy to the primary tumour[52] Local radiotherapy was mandated, unless contraindicated, for node negative disease and encouraged for node positive disease Radiotherapy was planned for 118/150 (79%) AAP & ADT patients and 57/74 (77%) docetaxel & ADT patients	**Metastasis-free survival** *Number of metastasis-free survival events* • AAP & ADT: 18/150 (12.0%) • Docetaxel & ADT: 10/74 (13.5%) HR 0.91 (95%CI 0.42 to 2.01) (p=0.824) **Progression free survival** *Number of failure-free survival events* • AAP & ADT: 13/150 (8.7%) • Docetaxel & ADT: 18/74 (24.3%) HR 0.34 (95%CI 0.16 to 0.69) (p=0.003) *Number of progression-free survival events* • AAP & ADT: 9/150 (6.0%) • Docetaxel & ADT: 10/74 (13.5%) HR 0.42 (95%CI 0.17 to 1.05) (p=0.064) **Important outcomes** **Symptom alleviation** *Number of symptomatic skeletal[53] events* • AAP & ADT: 5/150 (3.3%) • Docetaxel & ADT: 2/74 (2.7%) HR 1.28 (95%CI 0.24 to 6.67) (p=0.771) **Prostate cancer-specific survival** *Number of prostate cancer-specific deaths* • AAP & ADT: 6/150 (4.0%) • Docetaxel & ADT: 4/74 (5.4%)	1. Yes* 2. Yes* 3. Unclear 4. No* 5. No* 6. Unclear* 7. Yes 8. Unclear 9. Yes 10. Yes* 11. Yes* 12. Yes 13. Yes* **Other comments** STAMPEDE (Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) was a multi-arm, multi-stage platform trial assessing different treatment regimens for both metastatic and non-metastatic patients The authors state that the STAMPEDE trial "assessed both of these treatment approaches [AAP & ADT and docetaxel & ADT] separately

[52] This description of standard care is provided in the paper abstract. In the full text standard care is described as long term hormone therapy with luteinizing hormone-releasing hormone analogues (with short term antiandrogen if relevant) or orchidectomy. The details reported in the paper relate to both patients with metastatic and non-metastatic disease. It is not clear if any non-metastatic patients received orchidectomy

[53] This outcome was not defined by Sydes et al 2018 nor in other included STAMPEDE papers

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			HR 0.82 (95%CI 0.24 to 2.81) (p=0.751)	against the previous SOC [standard of care]". Stratified randomisation allocated patients 2:1:2 to standard of care; standard of care & docetaxel & prednisolone; or standard of care & abiraterone acetate & prednisolone. This paper reports an analysis comparing AAP & ADT and docetaxel & ADT. The patients included in this analysis were contemporaneously randomised to AAP & ADT or docetaxel & ADT between 2011 and 2013. The authors stated that there was no formal sample size calculation for this comparison The analysis was described as a "pre-specified (but not pre-powered) analysis using only patients who were randomised during a period of the study when recruitment to the research arms overlapped." However, it was also described as 'opportunistic' Limited information was provided specifically about the non-metastatic patients. It is not clear if the 2 groups were similar at baseline

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				No information was provided about the completeness of follow-up for these groups of patients No definition was provided for the outcome of symptomatic skeletal events in this paper. For further discussion of this outcome see James et al 2017 Some outcomes reported in this paper (e.g. on safety) were for a combined population of patients with metastatic and non-metastatic disease. Patients with metastatic disease formed 56% of the population. Only outcomes with separate reporting for non-metastatic patients have been extracted Data for this analysis were collected from 100 of the 111 participating sites in the UK and 5 sites in Switzerland **Source of funding:** See James et al 2017 for details of STAMPEDE funding

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; ICER: Incremental cost effectiveness ratio; IQR: Interquartile range; IV: Intravenous; m: Metre; mg: Milligrams; mL: Millilitre; ng: Nanogram; PSA: Prostate specific antigen; QALY: Quality-adjusted life year; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; UK: United Kingdom

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

Appendix G GRADE profiles

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?

For abbreviations and footnotes see end of tables.

Table 2. Abiraterone acetate and prednisolone (AAP) and ADT compared to ADT

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	AAP & ADT	ADT	Result		
Overall survival (1 RCT)									
Number of deaths (number, %) at median 85 months follow-up (IQR 83 to 96) (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	95/459 (20.7%)	142/455 (31.2%)	Statistically significantly fewer deaths with AAP & ADT HR 0.63 (95%CI 0.48 to 0.82) p=0.0005	Critical	Moderate
Number of deaths (number, %) at median 40 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) James et al 2017	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[1]	34/460 (7.4%)	44/455 (9.7%)	No statistically significant difference between groups HR 0.75 (95%CI 0.48 to 1.18) p not reported	Critical	Moderate
Metastasis-free survival (1 RCT)									
Number of metastasis-free survival events (number, %) at median 85 months follow-up (IQR 83 to 96) (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	111/459 (24.2%)	183/455 (40.2%)	Statistically significantly fewer events with AAP & ADT HR 0.54 (95%CI 0.43 to 0.68) p<0.0001	Critical	High

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**AAP & ADT**	**ADT**	**Result**		
Progression free survival (1 RCT)									
Number of failure-free survival events (number, %) at median 85 months follow-up (IQR 83 to 96) (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	120/459 (26.1%)	277/455 (51.0%)	Statistically significantly fewer events with AAP & ADT HR 0.39 (95%CI 0.31 to 0.49) p not reported	Critical	High
Number of failure-free survival events (number, %) at median 40 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) James et al 2017	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	38/460 (8.3%)	142/455 (31.2%)	Statistically significantly fewer events with AAP & ADT HR 0.21 (95%CI 0.15 to 0.31) p not reported	Critical	High
Number of progression free survival events (number, %) at median 85 months follow-up (IQR 83 to 96) (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	84/459 (18.3%)	166/455 (36.5%)	Statistically significantly fewer events with AAP & ADT HR 0.43 (95%CI 0.33 to 0.56) p not reported	Critical	High
Symptom alleviation (1 RCT)									
Number of symptomatic skeletal events (number, %) at median 40 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) James et al 2017	Serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[1]	11/460 (2.4%)	1/455 (4.2%)	No statistically significant difference between groups HR 0.56 (95%CI 0.27 to 1.18) p not reported	Important	Low
Prostate cancer-specific survival (1 RCT)									
Number of prostate cancer-specific deaths (number, %) at median 85 months follow-up (IQR 83 to 96) (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	No serious limitations	No serious indirectness	Not applicable	No serious imprecision	48/459 (10.5%)	86/455 (18.9%)	Statistically significantly fewer events with AAP & ADT HR 0.52 (95%CI 0.36 to 0.75) p not reported	Important	High

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	AAP & ADT	ADT	Result		
Safety (1 RCT)									
Adverse events ≥ Grade 3 (number, %) to 24 months follow-up (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	169/451 (37.5%)	130/455 (28.6%)	No statistical comparison between groups	Important	Moderate
Adverse events Grade 5 (number, %) to 24 months follow-up (benefit indicated by fewer events)									
RCT (STAMPEDE) Attard et al 2022	Serious limitations[3]	No serious indirectness	Not applicable	Serious imprecision[4]	3/451 (0.7%)	0/455 (0%)	No statistical comparison between groups	Important	Low
Reasons for permanently stopping AAP (number, %) to 24 months follow-up									
RCT (STAMPEDE) Attard et al 2022	Serious limitations[3]	Serious indirectness[5]	Not applicable	Not calculable	451	N/A	• Treatment complete: 266 (59%) • Excessive toxicity: 60 (13%) • Treatment refusal: 14 (3%) • Disease progression: 18 (4%) • Patient choice: 5 (1%) • Death: 3 (1%) • Clinician decision: 3 (1%) • Intercurrent illness: 1 (<1%) • Not stopped: 18 (4%) • Other (not further defined): 63 (14%)	Important	Low

Abbreviations

AAP: Abiraterone acetate and prednisolone; ADT: Androgen deprivation therapy; CI: Confidence intervals; HR: Hazard ratio; IQR: Interquartile range; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

1. Imprecision: Serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold
2. Risk of bias: Serious limitations due to lack of blinding for this subjective outcome
3. Risk of bias. Serious limitations due to lack of statistical analysis

4. Imprecision: Serious imprecision due to 0 events in the comparator arm
5. Indirectness: Serious indirectness due to no comparison across treatment arms

Table 3. Abiraterone acetate and prednisolone (AAP) and ADT compared to docetaxel and ADT

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	AAP & ADT	Docetaxel & ADT	Result		
Overall survival (1 RCT)									
Number of deaths (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[2]	16/150 (10.7%)	6/74 (8.1%)	No statistically significant difference between groups HR 1.51 (95%CI 0.58 to 3.93) p=0.395	Critical	Low
Metastasis-free survival (1 RCT)									
Number of metastasis-free survival events (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[2]	18/150 (12.0%)	10/74 (13.5%)	No statistically significant difference between groups HR 0.91 (95%CI 0.42 to 2.01) p=0.824	Critical	Low
Progression free survival (1 RCT)									
Number of failure-free survival events (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	No serious imprecision	13/150 (8.7%)	18/74 (24.3%)	Statistically significantly fewer events with AAP & ADT HR 0.34 (95%CI 0.16 to 0.69) p=0.003	Critical	Moderate
Number of progression free survival events (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[3]	9/150 (6.0%)	10/74 (13.5%)	No statistically significant difference between groups HR 0.42 (95%CI 0.17 to 1.05) p=0.064	Critical	Low
Quality of life (1 RCT)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	AAP & ADT	Docetaxel & ADT	Result		
Global quality of life score (EORTC QLQC30), difference between groups (95%CI) at 2 years follow-up (benefit indicated by higher score)									
RCT (STAMPEDE) Rush et al 2022	Very serious limitations[4]	No serious indirectness	Not applicable	Serious imprecision[5]	137	71	No statistically significant difference between groups Difference 3.0 points (favouring AAP & ADT) (95%CI -2.4 to 8.3) p=0.275	Important	Low
Symptom alleviation (1 RCT)									
Number of symptomatic skeletal events (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Very serious limitations[4]	No serious indirectness	Not applicable	Very serious imprecision[2]	5/150 (3.3%)	2/74 (2.7%)	No statistically significant difference between groups HR 1.28 (95%CI 0.24 to 6.67) p=0.771	Important	Very low
Prostate cancer-specific survival (1 RCT)									
Number of prostate cancer-specific deaths (number, %) at median 48 months follow-up (IQR not reported) (benefit indicated by fewer events)									
RCT (STAMPEDE) Sydes et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Very serious imprecision[2]	6/150 (4.0%)	4/74 (5.4%)	No statistically significant difference between groups HR 0.82 (95%CI 0.24 to 2.81) p=0.751	Important	Low

Abbreviations

AAP: Abiraterone acetate and prednisolone; ADT: Androgen deprivation therapy; CI: Confidence intervals; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: Hazard ratio; IQR: Interquartile range; RCT: Randomised controlled trial; STAMPEDE: Systemic Therapy for Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

1. Risk of bias. Serious limitations due to lack of clarity about the similarity between groups at baseline and uncertainty about whether follow-up was complete
2. Imprecision: Very serious imprecision due to very wide 95% confidence intervals that cross the default minimal clinically important difference lower and upper thresholds
3. Imprecision: Serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold
4. Risk of bias. Very serious limitations due to lack of clarity about the similarity between groups at baseline, uncertainty about whether follow-up was complete and lack of blinding for this subjective outcome
5. Imprecision: Serious imprecision due to wide 95% confidence intervals with an upper threshold that is higher than the minimal clinically important difference stated by the study authors (>4.0 points)

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it

	is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Time horizon	The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence.

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Included studies

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