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# Apalutamide treatment for nonmetastatic, castration-resistant prostate cancer

## A cost-effectiveness analysis of apalutamide plus androgen-deprivation therapy compared to androgen-deprivation therapy plus placebo


**List of abbreviations**

*AE* = adverse event.

*ADT* = androgen deprivation therapy.

*AIC* = Akaike information criterion.

*AUC* = area under the curve.

*BNF* = British National Formulary.

*CE* = cost-effectiveness.

*CEA* = cost-effectiveness analysis.

*CEAC* = cost-effectiveness acceptability curve.

*CLT* = central limit theorem.

*CUA* = cost-utility analysis.

*EMA* = European medicines agency.

*eMIT* = electronic market information tool.

*FDA* = food and drug administration.

*GnRHa* = gonadotropin-releasing hormone analogue.

*HCC* = half-cycle correction.

*HCRU* = health care resource use.

*ICER* = incremental cost-effectiveness ratio.

*ICUR* = incremental cost-utility ratio.

*KM* = Kaplan Meier.

*mCRPC* = metastatic castration-resistant prostate cancer.

*MF* = metastases-free.

*MFS* = metastases-free survival.

*NHS* = National Health Service.

*NICE* = National Institute for Health and Care Excellence.

*nmCRPC* = nonmetastatic castration-resistant prostate cancer.

*NSCLC* = non-small cell lung cancer.

*OS* = overall survival.

*PCa* = prostate cancer.

*PD* = progressed disease.

*PFS* = progression-free survival.

*PrSA* = probabilistic sensitivity analysis.

*PSA* = prostate specific antigen.

*PSSRU* = Personal social services research unit.

*QALY* = quality-adjusted life-year.

*QoL* = quality of life.

*RCT* = randomized controlled trial.

*SD* = stable disease.

*SE* = standard error.

*UK* = United Kingdom.

*US* = United States.

*WTP* = willingness to pay.

**Abstract**

The incidences of prostate cancer are rising due to various reasons. Much research is conducted to find new therapies with better clinical effects. Apalutamide is one of those new treatments; an anti-androgen that can be used for prostate cancer that has progressed to castration-resistant, or insensitive to hormone therapy such as androgen-deprivation therapy (ADT).

However, apalutamide is not the only new drug on the market and in order to ensure right and fair healthcare budget allocation, an economic evaluation was necessary to research the cost-effectiveness of apalutamide for nonmetastatic, castration-resistant prostate cancer (nmCRPC) combined with ADT, compared to placebo with ADT. This was done from a United Kingdom (UK) healthcare perspective. For this cost-effectiveness analysis, costs and utilities were gathered from literature and a Markov model was constructed in Excel. The model was based on the clinical SPARTAN-trial, from which clinical effectiveness, health care resource use and medication was derived. Costs and utilities were gathered from other literature sources with patient population similar to the SPARTAN-patients. A deterministic incremental cost-effectiveness ratio (ICER) was calculated, with several scenario analyses to estimate the impact of a changes in some variables. This was followed by the execution of a probabilistic sensitivity analysis which yielded probabilistic results of the ICER with incorporated uncertainties surrounding the model and its input parameters. This was visualised in a cost-effectiveness plane and subsequently in a cost-effectiveness acceptability curve which used several willingness to pay thresholds (WTP) to show the probabilities of the treatment being cost-effective for those varying thresholds.

The model resulted in a deterministic ICER of £101.854. This is above the UK-WTP-threshold of £30.000 per quality-adjusted life-year (QALY). The probabilistic results showed that, with this cost-effectiveness threshold of the UK, the probability that apalutamide + ADT is cost-effective compared to placebo + ADT, is low: 0.07 or 7%. The scenario analyses showed that a change in the utility of progressed, metastatic disease would have great impact on the ICER, as would a change in health care resource use costs in the progressed disease state or a reduction in the price paid for apalutamide. Adverse events are assumed to be of low impact on the ICER.

This cost-effectiveness analysis is surrounded by quite a few limitations, such as the varying validity of literature sources with different patient populations, choices that had to be made in the construction of the model and general limitations regarding (Markov) models. Regardless of the uncertainty, chances are very slim that reimbursing apalutamide + ADT as a treatment for nmCRPC would be cost-effective. Future research should compare the cost-effectiveness of different anti-androgens to each other or investigate the cost-effectiveness of apalutamide for hormone sensitive PCa.

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## 1. Introduction

Currently, prostate cancer (PCa) is the second most frequently diagnosed type of cancer in men throughout the world (1). 24% of all cancers diagnosed in 2018, were PCa diagnoses and the overall mortality rate is 10.1% in Europe. It is the sixth most prevalent cause of cancer related deaths among men (2). The incidence increases the higher the age category and is around 60% for men in the age category of 65 + years (1). It is estimated that one in eight men in the United Kingdom (UK) will receive the diagnosis PCa during their life (3). Due to the relatively high age of men that receive this diagnosis, the risk of death for those individuals from other causes is higher than the risk of death due to PCa (4). However, this does not mean that the disease has no effect on quality of life. Early detection through screening and adequate treatment for prostate cancer is desirable because incidences are increasing and, once metastasised, there is no curative treatment available. Prostate-specific antigen (PSA) testing is used for screening. Because elevated PSA-levels could also indicate other prostate-related diseases, the screening program is not recommended in the United Kingdom (UK). Nevertheless, it is still used on quite a broad scale on men who present with urinary tract or prostate symptoms to diagnose PCa (5). The increase of this PSA-testing accounts partly for the increase in PCa incidence. Additionally, an increase in life-expectancy causes an increase in prostate cancer diagnoses (6). According to Rawla, an increase in incidence of around 79.7% is to be expected in 2040 (1).

Treatment is different for every stage of PCa. For metastatic PCa, chemotherapy and androgen deprivation therapy (ADT) are often chosen, with potential (severe) adverse events and no prospect on remission (3). It is therefore favourable to prevent the disease from metastasising for as long as possible. ADT is also used in men with nonmetastatic PCa, to prevent metastases. After a brief effective period however, ADT-effects decrease because the tumour progresses into castration-resistant prostate cancer (CRPC). This entails that the tumour becomes insensitive to hormonal treatment. CRPC is associated with a shorter PSA-doubling time and shorter time to metastases and death (7). Metastases of PCa often spread to bones, which cause pain, pathological fractures and discomfort (8). Thus, by treating to prevent metastases, lifespan and quality of life will increase.

A significant increase in life-expectancy combined with the fact that there is no current treatment to prevent metastases from forming in nonmetastatic CRPC (nmCRPC), signifies the growing problem of prostate cancer for a modern, ageing society. It is crucial to prevent metastases to prevent deaths and a decrease in quality of life (QoL).

In 2018, the drug apalutamide, a nonsteroidal anti-androgen, was approved by the European Medicines Agency (EMA). This drug shows great potential for the treatment of nmCRPC. In CRPC, overexpression of androgen-receptors enhances the process of progression in PCa (9). Apalutamide

binds to these receptors and prevents numerous downstream processes that ultimately lead to progression (8). The main goal of this treatment is to prevent metastases from forming, which would prevent numerous deaths from PCa. Aside from apalutamide, there are two other drugs in this class: enzalutamide and darolutamide. According to Mori et al., out of those three, apalutamide is the most effective (10). This is why it is interesting to know the cost-effectiveness of apalutamide compared to placebo plus ADT for patients with nmCRPC, their doctors and decisionmakers.

However, the cost-effectiveness of apalutamide for nmCRPC has yet to be determined. This is essential to estimate, because apalutamide is not the only 'new' cancer therapy for that recently entered the market. Cancer research has been a hot topic in research for quite a while. Numerous new (cancer) treatments enter the market every year. Nevertheless, they are expensive, which poses difficult decisions for insurers, decisionmakers and governments: the available healthcare budget has to be allocated fairly. A cost-effectiveness analysis helps with a just allocation of the (limited) healthcare budget.

To provide tools to decide whether or not to reimburse apalutamide for nmCRPC-patients, a cost-effectiveness analysis was conducted in this thesis.

The aim of this research was to weigh the costs and effects of apalutamide combined with ADT. In order to do so, a cost-effectiveness analysis was provided in which apalutamide plus ADT will be compared to placebo plus ADT in terms of costs and effect from a healthcare perspective, namely that of the UK. The intervention is aimed at adult men suffering from nmCRPC with a high risk of developing metastases. The research question of this thesis is as follows:

*What is the cost-effectiveness of apalutamide plus androgen deprivation therapy as treatment for nonmetastatic, castration-resistant prostate cancer compared to androgen deprivation therapy plus placebo for adult men in the UK?*

## 2. Background

As mentioned in the introduction, apalutamide was approved by the EMA, which means that the drug is considered safe and effective (11). However, the EMA does not take costs into consideration. Hence, a cost-effectiveness analysis is necessary for healthcare budget allocation, for which country specific costs and utilities are desirable. This thesis did not conduct real-life research but instead collected information about effects and costs from different sources to construct a model. As for the clinical effects of apalutamide, a research conducted by Smith et al. was used as main source (8). Several literary sources were analysed in this chapter, followed by a brief explanation of types of economic modelling.

*The SPARTAN-clinical trial*

In 2018, Smith et al. published a randomized controlled trial (RCT) about the clinical effects of apalutamide treatment as add-on to ADT (8). This SPARTAN-trial was conducted in 26 countries at 332 sites. Patients included were a minimum of 18 years and histologically or cytologically diagnosed with castration-resistant adenocarcinoma of the prostate, with a high risk on the development of metastases. Patients with (distant) metastases were excluded. Imaging to detect metastases was performed every 16 weeks. Patients were randomly assigned to either the apalutamide group (N = 806) or the placebo group (N = 401). The primary endpoint in this study was metastasis-free survival (MFS). Secondary endpoints were time to metastasis, progression-free survival (PFS), time to symptomatic progression, overall survival (OS), time to initiation of cytotoxic chemotherapy. The MFS in the apalutamide group was 40.5 months, compared to 16.2 months in the placebo group (hazard ratio 0.28, 95%, CI: 023 – 0.35, $p < 0.001$). All secondary endpoints were significantly improved in the apalutamide group compared to placebo. In the intervention group, the secondary endpoint goal was never reached for overall survival. In the placebo group, this was 39.0 months. The hazard ratio was 0.70 (CI: 0.47 – 1.04). Since data on overall survival was not sufficient in this trial, Smith et al. reported the more mature results for OS and time to initiation of cytotoxic chemotherapy in another paper (12). This study concluded that apalutamide plus ADT therapy has clinical benefits over placebo + ADT.

It can be concluded that the clinical benefits of apalutamide treatment for nmCRPC seem to be quite apparent. However, next to the clinical benefits, costs should also be assessed thoroughly for an economic evaluation. In the UK, apalutamide is priced at £2735.00 per 112 tablets of 60mg, supplying 28 days of treatment. This cost-effectiveness analysis (CEA) sought to assess whether or not the clinical benefits worth the money in an objectifiable way.

*Previous cost-effectiveness evaluations*

In literature, several examples of economic evaluations regarding apalutamide and other anti-androgens were found. Here, a few will be briefly mentioned.

Firstly, Parmar et al. published a cost-utility analysis (CUA) of apalutamide for metastatic castration-sensitive prostate cancer as an add-on to ADT compared to solely ADT (13). This evaluation was performed from a Canadian perspective with a life-time horizon. The authors produced an incremental cost-effectiveness ratio (ICER), of $160,483 per quality-adjusted life-year (QALY), which is above the Canadian threshold of $100,000/QALY. The authors therefore concluded that apalutamide plus ADT was not likely to be cost-effective for mCSPC in Canada. The authors looked at a different disease state and at a different country than this analysis considered, thus this result could not be directly applied to the UK since utilities and costs can vary between countries. Those differences are essential for assessing the country-specific cost-effectiveness.

Secondly, Bin Riaz et al. performed a quite similar economic evaluation (14). They conducted a research about the cost-effectiveness of three novel anti-androgens, enzalutamide, darolutamide and apalutamide, compared to each other and to ADT in nmCRPC. They did so from a United States (US) healthcare payer perspective with a life-time horizon using a Markov state-transition model. They calculated both an ICER and an incremental cost-utility ratio (ICUR). They concluded that apalutamide + ADT was more cost-effective than enzalutamide + ADT with costs per QALY under the US threshold of $150,000/QALY. The costs of darolutamide-treatment were lower but apalutamide gained more QALYs in total. This research illustrated that apalutamide has the most QALY-gaining possibilities. However, the perspective and thus the costs are different from the research question of this thesis.

Next, Zhou et al. conducted research about the cost-effectiveness of apalutamide + ADT versus placebo + ADT from a US societal perspective (15). A Markov model with a life-time horizon and a cycle length of a month was constructed, based on the SPARTAN-trial as well. However, the authors failed to provide a conclusion about the cost-effectiveness of apalutamide + ADT compared to placebo + ADT because of insufficient long-term data. It does signify the importance of the publication of Smith et al, which does have long-term data on survival (12).

As mentioned before, enzalutamide is one of the drugs in the same class as apalutamide. The National Institute for Health and Care Excellence (NICE) has already conducted a cost-effectiveness analysis for enzalutamide in 2018, which was based on the PROSPER-trial (16). NICE found a deterministic ICER of £28.853, which classified as cost-effective (17). Additionally, Mori et al. notes that apalutamide is more effective than enzalutamide, which further increases interest in apalutamide (10).

To summarize previous literature, this thesis was not the first to assess the cost-effectiveness of apalutamide or a drug similar to it. However, the abovementioned literature does not provide an answer to the research question proposed, because the analysis was either performed in another country, it did not compare apalutamide to ADT + placebo or analysed the cost-effectiveness of a closely related drug. Therefore, a cost-effectiveness analysis with a model to assess the value of apalutamide in the UK was indicated as necessary.

*Economic models*

Since there is no real-life data on cost-effectiveness, this had to be estimated with the use of an economic model. There are several types of models, for instance, cohort models and microsimulation models. The latter focusses on individuals and variation within those individuals, while the first focusses more on variability in costs and effects for the average individual. Microsimulation models are used when the history of an individual is important in estimating the costs and effects (18). For this CEA, not enough data was available for a microsimulation because individual patient treatment history was not available. Therefore, cohort modelling was applied for this analysis. The two most common types of cohort modelling are the decision tree and the Markov model. Of those two, the decision tree is often regarded as the simplest and therefore relatively easy to apply, mainly due to the visual aspects of the model. On the other hand, the decision tree has several limitations. Firstly, the passing by of time is not easily visualised in a decision tree (18). Secondly, the more cycles that are necessary, the more difficult it becomes to understand a decision tree. The visuality of the model is a disadvantage in this scenario. In the disease this CEA is focussing on, it was hypothesised that many cycles were necessary since the time until progression and/or death can be long. On top of that, Markov modelling is especially useful to address complex uncertainties about variables and when a lot of cycles are indicated. It is often used in a long stochastic process, which is a random process that evolves over time, according to Briggs et al (18). The Markov state-transition model can be used for a cohort of patients with a long time-horizon, which is the case for this research question (19).

## 3. Research methods

The research question of this thesis was answered by estimating the cost-effectiveness, with effectiveness measured in utilities, to estimate the costs of additional QALYs (20). This CEA was visualised in an ICER which consist of the incremental costs and the incremental effectiveness of the intervention compared to the comparator. This ICER was compared to the cost-effectiveness threshold/willingness to pay of the National Health Service (NHS), which is £30.000 per QALY (21,22). To do this, the costs and the effectiveness of apalutamide plus ADT and its comparator were carefully researched. The way this research was conducted, is described in this chapter. All input parameters are shown in appendix 1.

### *3.1. Additional life-years and MFS*

As mentioned before, the goal of treatment with apalutamide is, primarily, prolonging metastasis-free survival (MFS) which is associated with a higher quality of life but also extending life-expectancy. For a model like the one of this thesis, it is preferred to use real-life patient data from a clinical trial to calculate the life-years and QALYs gained. Smith et al. provides a Kaplan-Meier (KM) curve that shows overall survival (OS) (12). However, they only provide information until the median OS is reached. This is the case because the SPARTAN-trial did not have a time horizon in which every patient died or progressed into metastatic disease. On top of that, no patient-level data is available.

For this analysis, a life-time horizon was preferred because it creates a full overview of the additional life-years, since the main goal of the researchers of SPARTAN was to increase MFS and OS with apalutamide (8). Since the SPARTAN-study does not provide that information, there was a need for extrapolating pseudo patient-level data with parametric survival analysis.

The first step in acquiring this, was to extract relevant X and Y points on the MFS and OS graphs with WebPlotDigitizer4.1 software (8,12). These numbers represent the pseudo-patient level data. Separate files were made for apalutamide and placebo and for MFS and OS of those two. The graphs used for this extraction are the graphs in figure 1 (MFS) and figure 2 (OS).

Following this, number at risk and relevant X and Y values were used to estimate number of deaths and censored patients given a time interval of 1 month. The median MFS of the placebo group from the extracted data was coherent with the median MFS given in the article, 16.2 months (8).

The area under the curve (AUC) was estimated following this extrapolation. In order to select the right extrapolation curve, the fit of the estimated curve was checked with the Akaike Information Criterion (AIC). The four possible extrapolation curves are exponential, lognormal, loglogistic and

Weibull. The optimal fit is often the function with the lowest AIC, provided that the curve is clinically plausible. Data on the Cholesky deposition was also obtained from R.

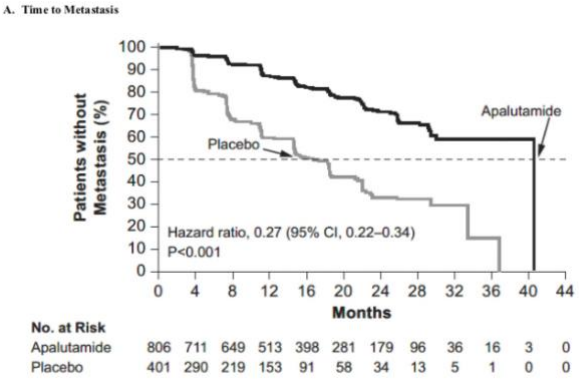


*Figure 1: MFS apalutamide & placebo (8)*

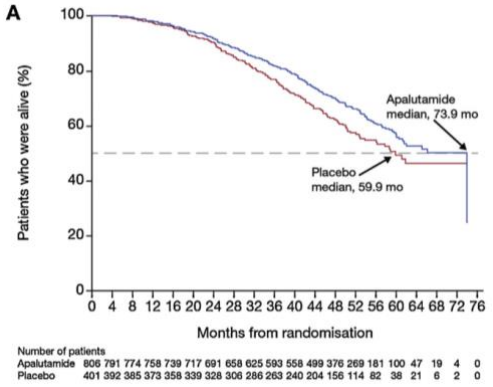


*Figure 2: OS apalutamide & placebo (12)*

### 3.2 Utilities

The effects were measured in utilities and expressed in (QALYs). To do so, additional life-years were multiplied by the utility of the health states of those years. Those utilities depended on the general state of health of both groups but were also (heavily) influenced by disutilities because of adverse events. The SPARTAN-trial does mentioned that they gathered patient-reported outcomes with the EQ-5D-3L questionnaire (15). This consisted of a descriptive system followed by a visual-analogue scale to validate health states, varying from 0 to 100. However, the authors did not provide (dis)utilities for every health state and adverse event (AE) incorporated in the model. Because of that, the additional, necessary data about utilities was derived from literature.

#### *3.2.1. Health-related quality of life*

Firstly, utilities were gathered for all relevant health states. The health states used in the model of this thesis, consisted of metastasis-free, progressed (metastatic) disease and death. The visualised model with health states can be found in figure 3. As one can see in figure 3, it is possible for a patient to either stay in the MFS-state, move to progressed disease or die after each cycle. When a patient's disease has progressed, the patient can either stay in progressed disease (PD) state or die. Once a patient entered death state, it is not possible to move to another health state. Group-specific utilities for nmCRPC were given in Saad et al., based on the SPARTAN-trial (23). The utility of the PD-state, mCRPC, was gathered from a study by Downing et al. (24). Downing et al. conducted a study about the quality of life of PCa-patients in the UK. The death state was given a utility of zero.

| *Health state* | *Utility apalutamide (source)* | *Utility placebo (source)* |
|---|---|---|
| *nmCRPC (MF)* | 0.762 (23) | 0.768 (23) |
| *mCRPC (PD)* | 0.717 (24) | 0.717 (24) |
| *Death* | 0 | 0 |

Table 1: utilities of health states

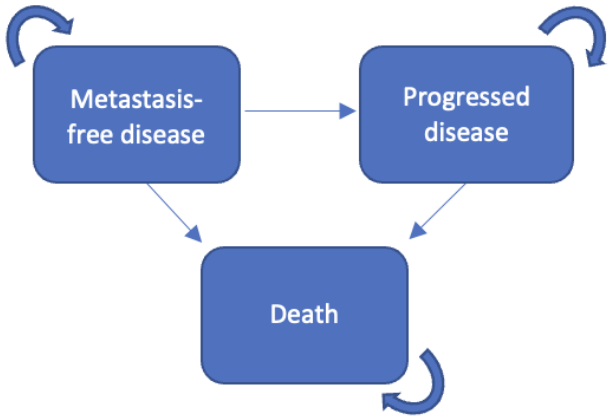


*Figure 3: Markov model: health states and transitions*

*3.2.2. Utilities lost due to adverse events (AEs)*

Secondly, disutilities had to be accounted for in this analysis to correct for any adverse events that occur during treatment with either apalutamide + ADT or placebo + ADT. To incorporate disutilities of adverse events in a model, the disutilities, duration of the AE and the probability of experiencing this AE were obtained. Adverse events of any grade present in at least 15% in either group were considered. This percentage has been chosen because the authors of the clinical trial only provided sufficient information about those adverse events (8). Other adverse events with lower incidences are mentioned in the supplementary appendix of Smith et al., but they lack details like severity, information that is considered necessary for incorporation in the model (25). If the adverse event had an incidence of >15%, regardless of the grade of severity, the probability of experiencing an adverse event of grade 3 or higher of that AE were used in the model. Those adverse events can be categorised as severe. Smith et al. found several other AEs noteworthy for various reasons, including the AE being strongly related to the treatment regimen or drug (8). Those AEs were dizziness, pathological fracture, hypothyroidism, mental-impairment disorder and seizure (8). Disutilities were not presented in the Smith et al. articles but were instead taken from articles and

prior CUAs or CEAs, such as the TA391 from NICE, or other scientific sources (17,25,26,27). For those values to be as close to 'true values' as possible, the patient-population of those sources was matched to the SPARTAN-population as closely as possible.

In table 3, the median disutilities, duration and the probabilities per group are listed. More detailed information on the probabilities of AEs regardless of the grade and with several standard errors (SEs) is provided in appendix 2.

| ***AE grades 3 or 4/special interest*** | ***Apalutamide*** | ***Placebo*** | ***Disutility (source)*** | ***Duration (source)*** |
|---|---|---|---|---|
| *Fatigue* | 0.9% | 0.3% | -0.094 (26) | 91.25 days (17) |
| *Diarrhoea* | 1% | 0.5% | -0.047 (26) | 8 days (26) |
| *Rash* | 5.2% | 0.3% | -0.03248 (28) | 60 days (25) |
| *Hypertension* | 14.3% | 11.8% | -0.153 (17) | 10.5 days (17) |
| *Weight loss* | 1.1% | 0.3% | -0.002 (29) | 90 days (27) |
| *Falls* | 1.7% | 0.8% | -0.069 (17) | 10.5 days (17) |
| *Pathological fracture* | 2.7% | 0.8% | -0.201 (17) | 30.42 days (17) |
| *Dizziness* | 0.6% | 0% | -0.125 (26) | 10.5 days (17) |
| *Hypothyroidism* | 8.1% | 2.0% | -0.1 (31) | 113 days (25) |
| *Mental-impairment disorder* | 5.1% | 3.0% | -0.06 (30) | 90 days (27) |
| *Seizure* | 0.2% | 0% | -0.06 (30) | 10.5 days (27) |

Table 2: disutilities, durations and probabilities

### *3.3 Costs*

The costs were determined for both the intervention and the comparator. The year 2021 was used as the reference year of those costs. In (the abovementioned) research, the authors obtain information about the costs and resource use from different sources. For example, Sathianathen et al. used the IBM Red Book database (19). However, those are US costs. Because costs are likely to be country-specific, this source was not relevant for this analysis.

The research question was answered from the NICE/NHS – UK perspective, a healthcare perspective. Therefore, only costs made by the NHS during treatment with either the intervention or the comparator were considered (32). These can be costs made during primary and secondary care but also during community services. Those medical costs include the costs of the drugs, hospital staff, other healthcare professionals, admissions and everything necessary during that, treatment of

adverse events et cetera. The SPARTAN-trial protocol provided detailed information on the resources used during the trial. Informal care and productivity costs were not considered in this analysis. The main article from Smith et al. mentioned more information about the medication regimens used (8).

Costs were mostly extracted from UK-governmental sites and resources, depending on what type of cost it concerned. Costs considered were drug acquisition costs including concomitant medication, health care resource costs, costs for the treatment of adverse events and end-of-life costs.

### *3.3.1 Drug acquisition costs*

According to Smith et al., apalutamide and the placebo were administered daily until either protocol-defined progression, severe adverse events or withdrawal of consent (8). Smith et al. defines protocol-defined progression as follows: “Time from randomization to the first detection of local or distant metastatic disease on imaging, as assessed by means of blinded independent central review, or death from any cause, whichever occurred first.” (8).

Costs for generic drugs, such as prednisone, were extracted from the electronic market information tool (eMIT) database because this database provides average costs of generics. According to NICE, this is more appropriate for generic drugs than the British National Formulary (BNF) (37). Costs of drugs that are not yet generically available, such as apalutamide (Erlaeda) and abiraterone acetate (Zytiga) were extracted from the BNF. Here, the most accurate information about what the NHS pays for (patented) drugs is listed.

All drugs used and its acquisition costs are mentioned in table 3. Concomitant medication was necessary in both the MF-state and the PD-state. For both the apalutamide and placebo group, an ADT is administered every day alongside the main therapy. On top of that, a gonadotropin-releasing hormone analogue (GnRHa) is used daily. The ADT that is mostly used in PCa, is bicalutamide and the most used GnRHa is Lucrin (33,34,35). Lucrin is injected once a day by the patient himself (34). Once patients develop metastasis and enter the progressed disease stage, they receive abiraterone acetate alongside prednisone and GnRHa (8,35). In appendix 3, a more detailed table can be found where the dosage and the package size are mentioned as well.

| ***Apalutamide – MF-state*** | | | ***Placebo – MF-state*** | | |
|---|---|---|---|---|---|
| *Drug* | *Costs* | *Source* | *Drug* | *Costs* | *Source* |
| *Bicalutamide* | £5.07 | (36) | Bicalutamide | £5.07 | (36) |
| *Apalutamide* | £2735.00 | (37) | | | |
| *Lucrin* | £75.24 | (37) | Lucrin | £75.24 | (37) |
| ***Apalutamide and placebo – PD-state*** | | | | | |
| *Drug* | *Costs* | *Source* | | | |
| *Abiraterone acetate* | £2735,00 | (37) | | | |
| *Prednisone* | £0,40 | (36) | | | |
| *Lucrin* | £75.24 | (37) | | | |

Table 3: drug acquisition costs

### *3.3.2 Health care resource use (HCRU) costs*

As mentioned in Smith et al., imaging was used to determine whether a patient had progressed (8). Other health care resources were used during the trial as well, to monitor the disease and overall health. According to the SPARTAN-protocol, the health care resource use was dependent on the cycle (38). The patients were screened at the start of their treatment. Health care resource regimens during the treatment varied. For example, haematology was tested every first day of every cycle, while computer topographies (CTs) were conducted once every 16 weeks, or once every 4 cycles. The exact regimens can be found in appendix 4. Of course, health care resources were still used during the progressed disease. During screening, physical examination was executed by a doctor since it had to be done thoroughly. During the other cycles, the nurse or assistant can execute the physical examination (23).

Costs for medical acts, hospital staff and other non-drug costs, were found in the NHS Reference Costs database from 2018/2019, the most recent publicly available database (39). Those costs had to be indexed to a year as close as possible to the reference year of this analysis, which is, as previously mentioned, 2021.

In appendix 5, an overview of all the costs for health care resources is provided. In table 4 below, the total health care resources use for every regimen is displayed. The calculations for these can be found in the costs sheet of the Excel file.

| ***Health care resource use regimen*** | ***Total costs*** |
|---|---|
| *Health care resource use screening* | £663,58 |
| *Health care resource use during every cycle* | £111,68 |
| *Health care resource use every 16 weeks* | £583,20 |
| *Health care resource use with PK-test* | £113,71 |
| *Health care resource use every 16 weeks plus PK-test* | £585,23 |
| *Health care resource use post-progression* | £508,00 |

Table 4: health care resource use costs for different regimens

### *3.3.3 Costs of adverse events*

In the supplementary index of Smith et al., all adverse events leading to treatment discontinuation, dose reduction and dose interruption were listed for the apalutamide group and the placebo group (25). Percentages of those were used in the model to estimate the costs of treating adverse events. However, Smith et al. did not mention how those adverse events were treated. Those costs for the treatment of AEs were collected from governmental sources and other sources such as other CEAs, whenever available. In the following table, table 5, the results are depicted. Costs of AEs that are not included in table 5, are that of nausea and arthralgia. Those did not cause grade 3 or 4 adverse events but are important for the scenario analysis later in this thesis. The costs of those AEs are £0 and £269 respectively (39).

| ***Type of AE*** | ***Costs AE*** | ***Sources*** |
|---|---|---|
| *Fatigue* | £354,00 | (26) |
| *Diarrhoea* | £400,00 | (26) |
| *Rash* | £0,35 | (39) |
| *Hypertension* | £1.849,00 | (39) |
| *Weight loss* | £0,00 | |
| *Falls* | £269,00 | (39) |
| *Pathological fracture* | £1.841,73 | (39) |
| *Dizziness* | £279,74 | (39) |
| *Hypothyroidism* | £919,82 | (39) |
| *Mental-impairment disorder* | £0,00 | |
| *Seizure* | £968,38 | (39) |

Table 5: costs of AE treatment

#### *3.3.4 End-of-life (EoL) costs*

EoL-costs are an estimated £5929,50, based on the average Table 1: (Estimated average cost of care services in the last twelve months of life) of the Personal Social Services Research Unit (PRRSU) 2019 (40).

### ***3.4 Markov-model***

Decision-analytical modelling is often used for the extrapolation of data from primary sources such as the SPARTAN-trial, when there is no further real-life data available (18). A model gives the likelihood of each consequence and its costs and benefits expressed in probabilities, which allows for a thorough analysis of cost-effectiveness without real-life data (18). As has been mentioned before in the background, there are several types of modelling. For the modelling of cost-effectiveness of apalutamide versus placebo, a Markov model was superior because of the complexity of uncertainties, number of cycles and variables, the use of a cohort of patients and the life-time horizon.

The model was synthesized with a cycle-length of four weeks and health states as mentioned before: metastasis-free survival, progressed disease and death. The model was designed to stop when every modelled patient reached death state. According to the NICE guidelines on technology appraisal, both the costs and the effects were discounted with an annual rate of 3.5% (32). This was

done in order to reflect the desire of the society to experience benefits of treatment now and face costs in the future. On top of that, half-cycle correction (HCC) was applied to estimate the unbiased life-expectancy (20). This only included the drug administration costs, since all drugs were taken daily. The HCRU-costs did not have to be HCCed, because they are only applied at the beginning of a cycle. With the Markov-trace, the deterministic ICER was estimated. The Markov model was made in Excel and provided separately from this document.

### *3.5 Probabilistic sensitivity analysis (PrSA)*

Many parameters, if not all, are uncertain to some extent, even though the information used for the model was as accurate as possible. In a probabilistic sensitivity analysis (PrSA), this uncertainty and the impact of those uncertainties were assessed.[1] On top of that, PrSA also lessens the effects of any biases because it reduces the impact of manipulation of data (18). PrSA does not assess any first-order uncertainty, or variability, which concerns differences between patients, but only structural uncertainty surrounding the model (18).

The deterministic parameters are all based on means. In PrSA, the distribution of data around that mean are recognised and analysed. SE plays a big role in that. The SEs of some parameters in this analysis were not known. In those cases, the SE was estimated. The way this was executed, depended on the type of parameter and could either be performed by calculating a percentage of the mean or by the following formula: SE = $\sqrt{p(1-p)/n}$, in which 'p' is the probability and 'n' the number of patients in the cohort (18).

The values of the mean and the SE of those parameters are all distributed in a certain pattern, for example, with a normal distribution. These distributions were not chosen at random for this analysis but based on arguments. Choosing a random distribution would only add up to the already existing uncertainty, as Briggs et al. argue (18). The best-known distribution is the normal distribution. However, this does not apply to most of the parameters included in this model because a normal distribution can only be applied to a parameter which follows the central limit theorem (CLT) (18). This means that the sampling of the mean will be normally distributed around the mean, independent of the underlying data. In other words: this could result in a sampled mean below zero or above 1, which is not (clinically) possible for some parameters such as probabilities. For example, a disutility has a range between 0 and 1. A normal distribution could indicate a disutility below 0, which is clinically impossible. For those values ranging between 0 and 1, a beta distribution is

[1] Usually, probabilistic sensitivity analysis is abbreviated as 'PSA'. However, since the abbreviation PSA is already used in this analysis for 'prostate specific antigen', the abbreviation 'PrSA' is chosen to prevent any confusion.

applied. For costs, which, in theory, can be anywhere between 0 and infinity, a gamma distribution is most accurate.

Following these distributions, repeated random (correlated) draws were made from the parameters, which resulted in a cost-effectiveness plane (CE-plane). It consists of four quadrants, of which the horizontal axis represents the difference in clinical effectiveness and the vertical the difference in costs between two treatments. Each dot represents a randomly generated incremental cost-effectiveness ratio (20). Ideally, a treatment is more effective and less costly: this is represented as a dot in the lower right quadrant. The least ideal situation is a dot in the upper left quadrant which means that the drug is more expensive but less effective.

The CE-threshold (λ) of a country is the WTP that a country decided upon for incremental health benefits. For the UK-government, it is interesting to investigate the probability of apalutamide being cost-effective for different WTP-thresholds. In theory, the higher the λ, the more dots are observed below the λ. However, as mentioned before, in a scenario where apalutamide is more costly, but less effective, it is highly unlikely that this treatment will be seen as cost-effective. Every decisionmaker would opt for a cheaper treatment with more clinical benefits. In a cost-effectiveness acceptability curve (CEAC), the probabilities of the treatment being cost-effective for several thresholds is visualised. These probabilities are of great importance for decisionmakers since it represents the probability of them making a decision that will yield cost-ineffective results.

### *3.6 Scenario analyses*

Lastly, after assessing the uncertainties surrounding the parameters in 1000 random draws with PrSA, several scenario analyses were conducted to explore the effect of change in one specific parameter at a time. These scenarios were conducted on aspects of the model that brought a substantial amount of uncertainty. The first scenario that was explored, is a scenario where the utility of the progressed disease is altered, both lower and higher. The utility of the MF-state was assessed during the SPARTAN-trial and is therefore considered to be a quite accurate portrayal of reality, aside from the fact that a trial itself never reflects reality perfectly. The PD-state utility is much more uncertain than that of the MF-state because it is not based on QoL-data extracted from the SPARTAN-clinical trial.

As mentioned before, only adverse events that are of grade 3 or higher are considered in the model. However, that does not mean that the other adverse events of lower grades have no impact. Costs of the adverse events were not specifically for severe (grade 3 or 4) reactions. Therefore, the second scenario conducted, is a scenario where the probabilities of having an AE are changed to the probabilities of experiencing an AE of any grade.

Furthermore, the costs for apalutamide are relatively high compared to other drug acquisition costs. In the future, these costs might decrease. For example, when negotiated with the UK-government or when the patent expires and apalutamide becomes a generic drug. This last scenario would not happen any time soon in real-life given the length of patents on drugs. Still, this analysis did show the effect of a price deduction.

Then, it would be interesting to observe the effect a price reduction or increase of one single adverse event at a time. Quite a few of those costs, especially the ones that were estimated using the NHS Reference Costs 2018/2019, are associated with uncertainty. So, this scenario is explored during one of the scenario analyses. Only the adverse events with relatively high treatment costs will be included in this scenario analysis. Those include fatigue, diarrhoea, hypertension, pathological fracture, hypothyroidism and seizure.

Finally, since the health care resource use costs are all estimates and averages, the last scenario that was conducted, consisted of changing the HCRU-costs in MFS and PD separately. This was applied to the total costs, not the individual parameters of which those HCRU-costs consist. In the PDS, a bigger change of 20% is applied because those modelled costs are expected to be most deviant from real-life costs. Since the protocol of SPARTAN does not mention if the health care resources are used only once after progression, every 4 weeks after progression or every 16 weeks after progression, a scenario was explored where those costs were only applied every 16$^{th}$ cycle (41).

## 4. Results

In this chapter, the results of literature research, extrapolation, the deterministic ICER and the probabilistic results are presented.

### *4.1 Extrapolation of Kaplan-Meier Curve*

As mentioned before, following the R-output, information about the AICs of the different extrapolations is gathered (table 1). The entire R-output is included in appendix 6.

| | MFS | | OS | |
|---|---|---|---|---|
| | ***Apalutamide*** | ***Placebo*** | ***Apalutamide*** | ***Placebo*** |
| *Exponential* | 1909.89 | 1545.286 | 2768.99580250184 | 1555.78051149994 |
| *Weibull* | 1874.627 | 1532.478 | 2631.91385659606 | 1484.44407939418 |
| *Lognormal* | 1869.353 | 1504.356 | 2632.74379913479 | 1483.50195231431 |
| *Loglogistic* | 1872.51 | 1520.017 | 2630.29320329682 | 1481.01531969706 |

Table 6: R-output

Usually, the extrapolation with the lowest AIC is considered as best-fit for the extrapolation of the KM-data. In the case of MFS, that would be lognormal and in the case of OS it would be loglogistic. However, the extrapolation should be clinically possible. Following the R-output, the extrapolation for all four curves was executed which yielded interesting results. For example, the chance of metastasis free survival for the apalutamide group with a lognormal extrapolation is 0.8% after 655,38 months, which is close to 54 years. Given the median age of 74 years in the apalutamide group, it is highly unlikely that this is clinically possible that 8 individuals are still alive without metastases (8). Furthermore, what is clear in all four graphs produced with the extrapolated data, is that none of the curves except Weibull reach an OS or MFS of 0. All four graphs are visible in figure 4 (MFS) and figure 5 (OS). This means that none of the other graphs are clinically possible. For this analysis, it is therefore decided that Weibull is chosen as extrapolation for MFS and OS for both groups.

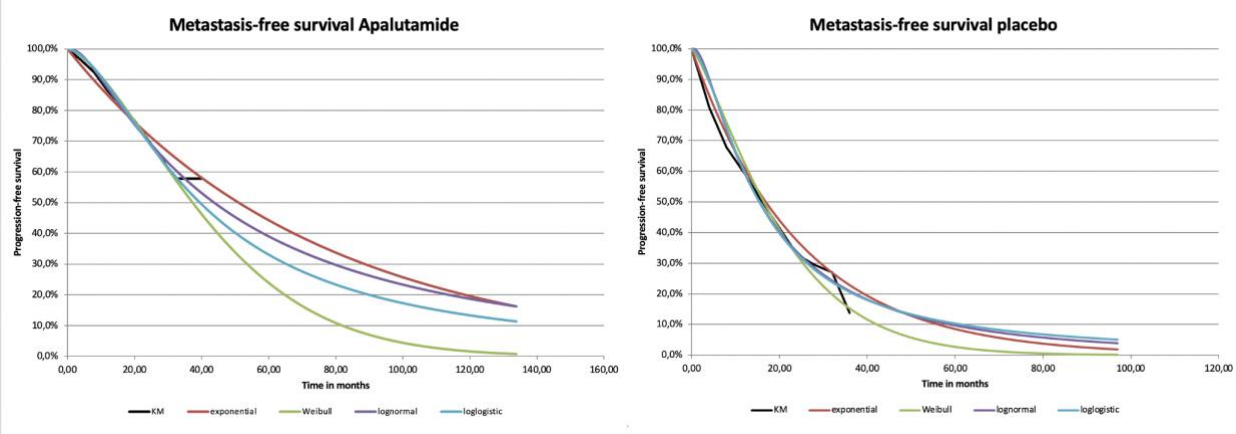


Figure 4: MFS-curves apalutamide and placebo

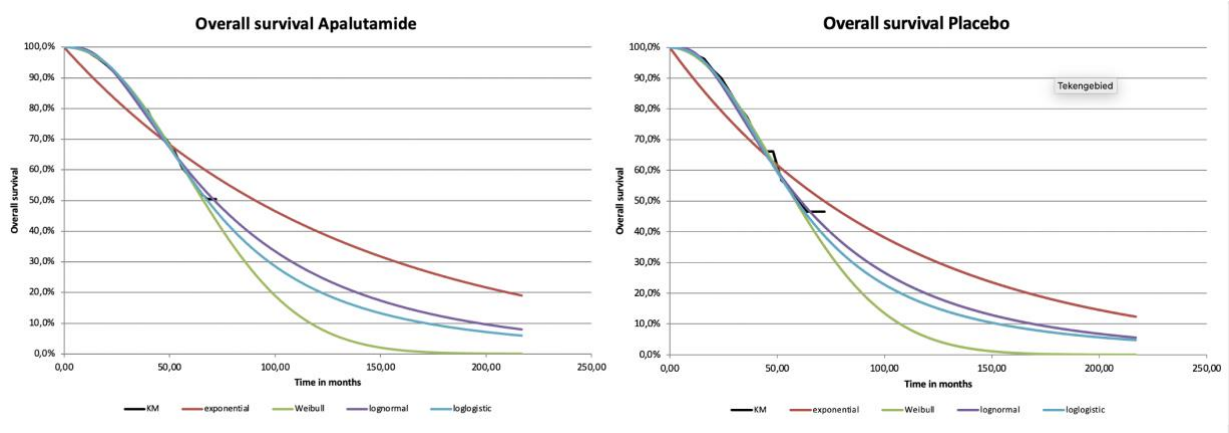


Figure 5: OS-curves apalutamide and placebo

### *4.2 Life-years and utilities*

As mentioned before, information about the probabilities, duration and disutilities of AEs were gathered from different sources. From this, the total disutilities for apalutamide + ADT and placebo + ADT were calculated. The results are shown in table 7 below. This table also shows the life-years accrued in both states of both groups, as well as the QALYs. As is noticeable, apalutamide-treatment mainly provides additional life-years and QALYs in the MF-state, and the placebo-treatment in PD-state.

| | ***Apalutamide + ADT*** | ***Placebo + ADT*** | ***Increment*** |
|---|---|---|---|
| *Life-years accrued in MF-state* | 3,56 | 1,69 | *1,87* |
| *Life-years accrued in PD-state* | 2,24 | 3,51 | *-1,27* |
| *QALYs accrued in MF-state* | 2,72 | 1,30 | *1,41* |
| *QALYs accrued in PD-state* | 1,60 | 2,70 | *-1,09* |
| *QALYs lost due to adverse events* | 0,004907522 | 0,001825417 | *0,003082105* |

Table 7: total (dis)utilities, QALYs and life-years per patient

### *4.3 Costs*

After gathering information about all costs, the costs were implemented in the model. The following table, table 8, provides information about the costs in the base-case analysis. The results are in accordance with the information from table 7: costs are higher for apalutamide in the MF-state and higher for placebo in PD-state.

| | ***Apalutamide + ADT*** | ***Placebo + ADT*** | ***Increment*** |
|---|---|---|---|
| *Drug acquisition costs MF-state* | £159.459,86 | £15.578,80 | *£143.881,06* |
| *Health care resource use MF-state* | £10.037,49 | £5.268,90 | *£4.768,59* |
| *Adverse event treatment costs* | £1.988,77 | £1.887,46 | *£101,30* |
| | | | |
| *Drug acquisition costs PD-state* | £99.990,94 | £156.925,18 | *-£56.934,24* |
| *Health care resource use PD-state* | £14.776,19 | £23.189,67 | *-£8.413,48* |

Table 8: cost components per patient

### *4.4 Deterministic ICER and disaggregated results*

Following the construction of the Markov model, the deterministic ICER was calculated. In table 9, the costs for apalutamide + ADT and placebo + ADT are presented, alongside the QALYs and life-years. In appendix 7, the disaggregated results from the deterministic ICER can be regarded. The deterministic ICER that followed was **£101.854** per QALY gained.

| | **Apalutamide + ADT** | **Placebo + ADT** | **Increment** |
|---|---|---|---|
| *Costs* | £258.239,06 | £182.639,85 | *£75.599,21* |
| *QALYs* | 4.31 | 3.57 | *0.74* |
| *Life-years (LY)* | 21.01 | 17.51 | *3.50* |

Table 9: deterministic costs

### *4.5 PrSA and CEAC*

After determining the deterministic ICER, the PrSA was performed. Figure 6 shows the resulting CE-plane with the probabilistic results. As can be seen in figure 6, all dots fall in the upper quadrants. This means that for every random draw of 1000, apalutamide + ADT was more expensive than placebo + ADT. Importantly, multiple dots lie in the upper left corner, which means that for those random draws, apalutamide + ADT was more expensive but less effective. This is a scenario that is not desired by clinicians, patients and decisionmakers.

After the PrSA, a cost-effectiveness acceptability curve was formed to explore the effect of an ascending WTP-threshold (λ). This can be seen in figure 7, where it is visible that the line reaches a plateau around 0.74. This means that, even with a willingness to pay threshold of over £600.000 per QALY, the probability of the treatment being cost-effective is only around 74%. Since the CE-threshold of the UK is £30.000 per QALY, the graph indicates that the probability of making the right decision when reimbursing apalutamide + ADT is 0.07, or 7%. For a threshold that is roughly equal to the deterministic ICER, this probability is around 0.47, or 47%.

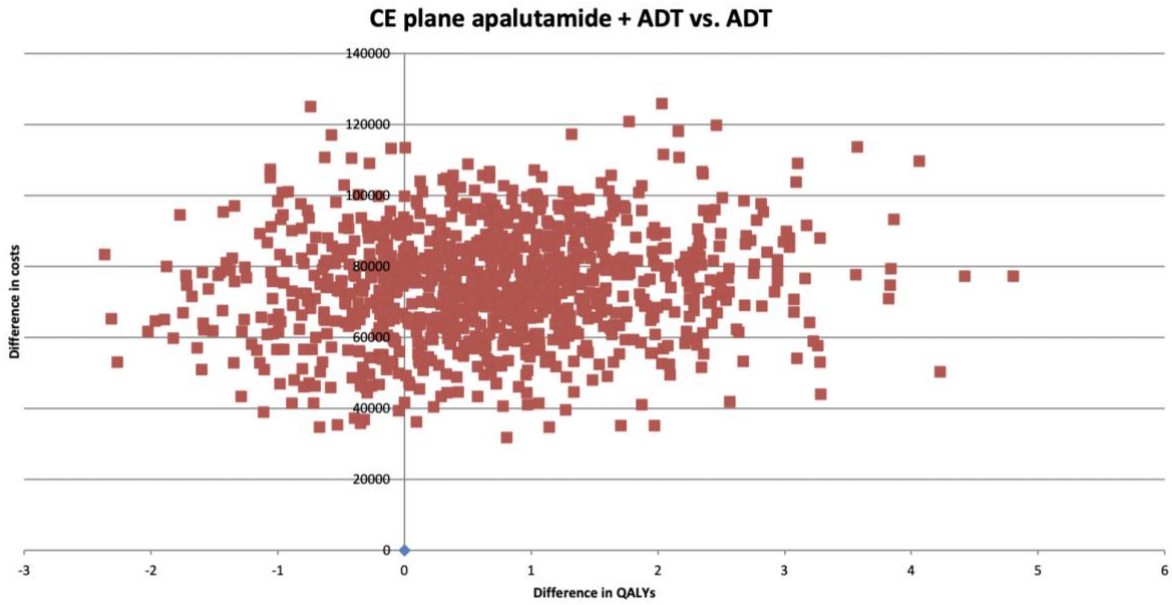


Figure 6: CE-plane apalutamide + ADT vs. placebo + ADT

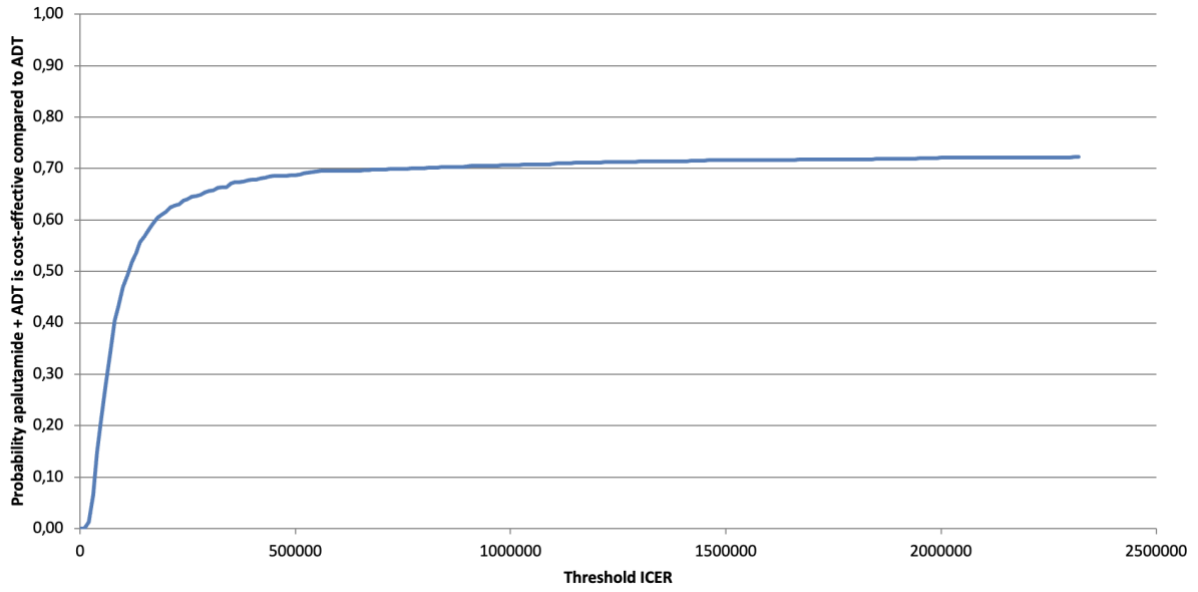


Figure 7: CEAC of apalutamide + ADT versus placebo ADT

### *4.6 Scenario analyses*

The last step of testing the cost-effectiveness of apalutamide and assessing its uncertainties, is the performance of several scenarios. Those included: a change in the utility of the PD-state, the inclusion of the probabilities of grade 1 and 2 adverse events, changes in the drug acquisition costs of apalutamide and lastly a change in AE-treatment and HCRU-costs. Results are addressed in table 8. In many cost-effectiveness analyses, the type of extrapolation is changed to see how that impacts the

ICER. However, given the observations made during the extrapolation process, which were mentioned in the 4.1 of this thesis, this is impossible. As can be seen in the table, a change in PD-utility and drug acquisition price of apalutamide had a great effect on the ICER, while a change in AE-costs or probabilities did not. A change in HCRU-costs did have an effect, but not as significant as a change in PD-utility.

| **Scenario** | **ICER** | **Change in ICER compared to base-case** |
|---|---|---|
| *Base-case* | £101.853,23 | |
| *Utility PD + 10%* | £83.751,29 | *-£18.102,04* |
| *Utility PD – 10%* | £129.937,91 | *+£28.084,68* |
| *Drug acquisition price apalutamide + 10%* | £117.494,21 | *+£15.640,98* |
| *Drug acquisition price – 10%* | £86.212,25 | *-£15.640,98* |
| *AE's any grade* | £102.618,07 | *+£764,94* |
| *Costs treatment AE fatigue + 10%* | £101.853,52 | *+£0,29* |
| *Costs treatment AE fatigue - 10%* | £101.852,95 | *-£0,28* |
| *Costs treatment AE diarrhoea + 10%* | £101.853,50 | *+£0,27* |
| *Costs treatment AE diarrhoea - 10%* | £101.852,96 | *-£0,27* |
| *Costs treatment AE hypertension + 10%* | £101.853,23 | *£0* |
| *Costs treatment AE hypertension - 10%* | £101.853,23 | *£0* |
| *Costs treatment AE pathological fracture + 10%* | £101.857,95 | *+£4,72* |
| *Costs treatment AE pathological fracture - 10%* | £101.848,52 | *-£4,71* |
| *Costs treatment AE hypothyroidism + 10%* | £101.860,79 | *+£7,56* |
| *Costs treatment AE hypothyroidism - 10%* | £101.845,67 | *-£7,56* |
| *Costs treatment AE seizure + 10%* | £101.853,49 | *+£0,26* |
| *Costs treatment AE seizure – 10%* | £101.852,97 | *-£0,26* |
| *HCRU-costs MFS + 10%* | £102.426,98 | *+£573,75* |
| *HCRU-costs MFS – 10%* | £101.279,48 | *-£573,75* |
| *HCRU-costs PD + 20%* | £87.786,97 | *-£14.066,26* |
| *HCRU-costs PD – 20%* | £115.919,49 | *+£14.066,26* |
| *HCRU-costs PD every 16$^{th}$ cycle* | £111.620,25 | *+£9.767,02* |

Table 8: effects of scenario analyses

## 5. Discussion and conclusion

To conclude, the deterministic ICER of apalutamide + ADT compared to placebo + ADT is £101.854 per QALY. This is above the WTP threshold of the UK of £30.000 per QALY. This means that the treatment is not considered cost-effective, regardless of the additional 0.74 QALY that is associated with it. The deterministic ICER does not account for uncertainties, which were addressed in the PrSA. As can be concluded from the CE-plane in figure 6 and the CEAC in figure 7, it is apparent that there is always a probability of making a decision that is not cost-effective, irrespective of the WTP-threshold. For UK-decisionmakers to reimburse apalutamide by viewing it as cost-effective, a serious price deduction of apalutamide should be negotiated by the UK government. However, it is fairly unimaginable that Janssen Pharmaceutica will accept a price deduction that serious.

This outcome of apalutamide not being considered cost-effective can be explained due to the fact that the incremental QALYs are only 0.74 in the deterministic effects and are thus sensitive to small uncertainties in the input utilities. The reason why the incremental QALYs are relatively low, is probably because there is no great difference between the utilities of MF-state and PD-state. This hypothesis is tested in a scenario analysis, where indeed the effect of a PD-utility of -10% has quite an impact on the ICER.

Next to the utilities being of impact, the costs are also of great influence. It is quite apparent that the drug acquisition costs in the MF-state are higher for apalutamide than for placebo. The impact of the price of apalutamide is shown in one of the scenario analyses. A price reduction or increase of 10% would change the ICER with £15.640,98. In the case of the reduction, this means that the ICER would be £86.212,25. It should be noted that the drug acquisition costs in the PD-state are higher for the placebo group because apalutamide patients remained in the MF-state longer (table 8). This is in accordance with the clinical results from Smith et al. (8). Ultimately, this means that the patients receiving placebo remained in the progressed state longer and thus had more costs and life-years there. This observation is also visible in the HCRU-costs, which are higher for apalutamide in MF-state and higher for placebo in PD-state for the same reasons as mentioned above. Scenario analyses showed the substantial impact of a reduction or increase of the costs in HCRU on the ICER, especially in PD.

Some parameters were not associated with much impact on the ICER. An example of this, are the adverse events. The deterministic increment of AE-costs is only £101,30**.** On top of that, a higher probability of those AEs altered the ICER with roughly £800 in one of the scenario analyses. Changing individual costs of AE-treatment often changed the ICER with only a few pounds.

Furthermore, this analysis and the sources on which it is based have some limitations. Those can be attributed to Markov modelling in general, the extrapolation, the SPARTAN-trial, utilities, costs and PrSA.

Firstly, modelling tries to represent real-life as accurately as possible, but it remains a model and is therefore not a perfect imitation. This is a limitation of a modelled CEA in general. Reflected in this fact, is that models use pseudo-level patient data and no real patient data. This means that there is no room for individual variation and/or history. However, history could be important if you want to know how many patients entered the PD-state before entering death-state, for example. A Markov model cannot address individual variation but as a clinician or decisionmaker, it is important to keep in mind that this could have implications on a certain patient population. Another example like this considers the probabilities of AEs. It should be mentioned that it is not known if the probability of experiencing a second, third (or more) AE decreases or increases if a patient has already experienced one AE. It is assumed that this has no effect on the ICER, but it could be important for the individual patient. Using a valid main clinical trial with as much information as possible, is essential in the process of representable sampling of the patient group.

This is important because the analysis is based on one trial, SPARTAN in this case (8). The validity of this article had to be critically assessed since both KM-curves were extracted from this article. In general, the trial was conducted in a valid way. Still, it should be remembered that, since this is based on one trial only, the extrapolation is only based on one sample. It is important that the sample is an accurate representation of the general patient population. This CEA was performed from a UK-health care perspective. Notwithstanding, the SPARTAN-trial was conducted in 332 sites in 26 countries across North America, Europe and the Asia-Pacific region. It is deemed possible that this could affect the outcome of this CEA. It is not possible to know how, because it could affect extrapolation through KM-curves, but also HCRU, adverse events and utilities.

Thirdly, some limitations arose during the analysis concerning utilities. Firstly, the utilities of the MFS of both groups were based on the SPARTAN-trial and are therefore deemed appropriate. It should be noted that the SPARTAN-trial measured total average utility throughout every cycle (8). However, Smith et al. did not distinguish progressed individuals from metastasis-free individuals. The researchers only did so at the baseline of the trial because every individual was metastasis-free at inclusion. It was therefore impossible to recover cycle- and health state-specific utilities, which are indispensable to ensure correct implementation of those data. In contrast to the utilities of the MF-state, the utility of PD-state was much more uncertain because it had to be extracted from secondary literature, in this case a population-based study conducted in the UK (24). As can be seen in the scenario analysis, this has quite some impact. It is thus a fairly big limitation to this CEA that the PD-utility is not extracted from the same group as the KM-curves and MFS-utility.

Next to the utilities, the disutilities caused some limitations as well. First, a slight irregularity was spotted when comparing the supplementary appendix to the main article (8,25). Somewhat deviant AEs were listed in those articles. For this analysis, the information about the AEs that was described in the main article was followed since this was more extensive. It remains unclear why the probabilities differed between the two articles.

On top of that, the values of the disutilities and the duration of those AEs are surrounded by quite some uncertainties because several assumptions had to be made. All the disutilities were extracted from literature other than the article by Smith et al. (8). Most disutilities were found in CEAs or other papers concerning PCa (both nmCRPC and mCRPC), but some were found in articles concerning non-small cell lung cancer (NSCLC), such as rash (17,25,26,27). All studies but one were conducted in the UK (29). Furthermore, based on a study, it was concluded that that seizure and mental impairment disorder were given the same disutility (30). However, the impact of both is very dependent on the severity and not much information was provided about that matter in Smith et al. (8). The disutility is relatively low compared to weight loss for example. Thus, it is suspected that in real-life, this will have more impact on patients than for which is assessed in this model. Lastly, the disutility of hypothyroidism is based on a decision-analytical model about (sub)clinical hypothyroidism as a primary disease in elderly, not an AE (31). Durations of AEs were mainly gathered from the same sources and when unknown, from Robertson et al (27). As can be concluded from this paragraph, the disutilities and duration of very different sources which could be remarked as an apparent limitation. Nevertheless, seeing the marginal impact of AE-probability, disutility and duration on the deterministic ICER during the scenario analyses, this is suspected to be limitation with a relatively small impact.

Following the utilities of AEs, several assumptions regarding costs were made as well. Most costs were extracted from the same sources as the utilities, for example the NICE reports (17,26). Other costs were extracted from the NHS Reference Costs 2018/2019 and are average UK-costs and thus considered accurate. However, one big assumption was done for the costs of mental-impairment disorder. No relevant NHS Reference Costs could be found for this AE and in the article of Smith et al., it was mentioned that this AE would stop the patient from participating (8). It is assumed that there is no treatment for this AE. Nevertheless, most patients with a mental-impairment disorder often require help from a nurse at home or any other form of guidance which would raise the costs. Nonetheless, those costs are not included in the healthcare perspective chosen for this analysis. Furthermore, the costs for rash were estimated using several drugs from the NHS Reference Costs 2018/2019 (39). It was not possible to include all drugs in this calculation but the impact of the inclusion of other drugs would not be severe, considering the low price of this

range of drugs (42). Once again, the impact of the limitation concerning AE-costs, is not suspected to be big following the same reasoning as for the utilities.

Next to the costs for AEs, the EoL-costs were gathered from the PSSRU (40). The costs are based on general UK-population. It could be the case that the end-of-life costs for the specific patient group of this analysis are somewhat higher or lower. On top of that, the EoL costs as an average of the costs spent in the last 12 months of life. The EoL-costs in this model are applied on a 4 week-cycle and not HCCed. Since there is no record of the costs per cycle or month, it is not possible to model this in any other way. Besides, this would not make any difference for the ICER considering the fact that EoL-costs of both groups is equal.

Since costs for HCRU are of significant impact on the difference in costs for apalutamide and placebo in MF- and PD-state, it is important to address any limitations regarding these costs. For the estimated costs of physical examination, the NHS Reference Costs of an oncologist and a urologist were averaged, for example. No exact value could be found in governmental sources or other literature. Next to that, a high number of tests is performed every cycle. The costs were gathered from the NHS Reference Costs, but it remains unclear whether, for example, PSA-testing is surely included in 'Clinical Biochemistry' (39). On top of that, it is assumed that the costs for imaging also include the assessment by a clinician. These are seen as the assumptions of this model with the most serious consequences, seeing the effect it could have on the deterministic ICER. Unfortunately, this was the most accurate information available at the time of this analysis.

Since, as mentioned before, the protocol of SPARTAN does not mention if the health care resources are used only once after progression, every 4 weeks after progression or every 16 weeks after progression, an assumption had to be made for that as well because a patient will still receive care after progression in real-life (41). As is known, a Markov model does not allow for individual patient history. It is therefore impossible to know if the patients in PD during cycle 12, are (partly) the same patients as in cycle 11. For the EoL-costs, the number of patients in death-state from the current cycle were subtracted from those in the previous cycle. This way, only patients that entered the death-state during that specific cycle were given the EoL-costs. The difference between this state and PD; the PD-state is not an end-state, which makes this EoL-technique inapplicable. Another option was to only apply HCRU-costs every 16 weeks in the PD-state. In this scenario, patients who moved from MFS to PD to death in a shorter timespan than 16 weeks, would not have been recognised in the calculation of the HCRU-costs of the PD-state and estimated costs would be lower. The last option was to apply costs the same way as has been done with AE-costs and disutilities. However, that option is already suboptimal for the AEs. In real-life, AEs do not occur solely in one cycle and on top of that, the costs, when necessary, cannot be HCCed. Considering the fact that every patient has the same probability of encountering one or multiple AEs, this is the best option for

modelling AEs. This does not apply to HCRU-PD-costs, since it is unknown how many patients have been in this state and for how long. Thus, none of the options are perfect and it is recognised that this could have serious implications for the ICER. Unfortunately, there was no better option. It must be noted that the ICER would most likely not become lower than the WTP-threshold. So regardless of how HCRU-costs are modelled, this would not impact decision-making severely.

The main source of costs in the apalutamide group, were the drug acquisition costs. No detailed information was provided in the article about the ADT and concomitant medication which created the necessity to make assumptions (8). Bicalutamide is chosen as the ADT, because the supplementary appendix mentions this drug briefly and on top of that it is mentioned in the NCCN guideline on prostate cancer (25,43). A different drug and a different dosage could result in a different price, but considering the fact that ADT is used regardless of group, a change in these costs would not impact the ICER severely. It should be noted that time spent in MFS is greater in the apalutamide group, so a cheaper ADT could decrease the ICER. The same holds up for the choice of the GnRH analogue, Lucrin, abiraterone acetate and prednisone. No specific drugs were mentioned in the SPARTAN-trial, neither were dosages or application methods. No extensive enough information was found in the NCCN guidelines or scientific literature. Therefore, Dutch prostate cancer guidelines were considered (35,44,43). The guidelines between countries can vary, which could impact the ICER, especially because the costs of abiraterone acetate are quite high. It is preferred to use guidelines of the UK, but those did not suffice. Since the Netherlands is a western country, the assumption was made that those guidelines would be relatively equal but some impact is not ruled out. One last remark about the modelling of the costs of Lucrin, is the number of dosages a patient could retrieve from one package. There is 3.75mg in one package, and a dosage of 1mg/day is assumed. Since the patients must inject themselves with this solution made with powder, it is assumed that some of the drug is wasted. Therefore, it is assumed that one package lasts 3 days. This assumption is done for all groups and cycles, regardless of disease stage and thus suspected to have no impact on the ICER.

In general, all costs gathered from the NHS Reference Costs were from 2018/2019. But as mentioned before, this analysis was written from the 2021 perspective. Costs from 18/19 were indexed to 19/20, but no indices were available yet for 2020/2021 (40). This effect could not be too extensive, however, one important event took place in 2020 that can greatly influence prices and availability: the Brexit. According to Godlee et al., the Brexit could have detrimental effects on healthcare: from shortages of drugs to insufficient supply of devices and problems in staffing (45). All these factors can contribute to a shortage of health care in general and thus increase prices (45). The index of 20/21 is thus expected to be different from years before and the impact is still unknown.

Finally, some remarks must be made concerning the overall modelling in this analysis and the PrSA. Firstly, in the model, it was possible to move from MF to PD and thus progress during every cycle, which mimics the natural behaviour of the disease. Yet, in the article, Smith et al. describe that a CT-scan was performed every 16 weeks to detect distant metastases and find out if a patient had moved from MF to PD (8). The difference between the model and the article could make a difference in HCRU-costs. In real-life, patients undergo a CT-scan every 16 months and, once a (distant) metastasis is found, stop apalutamide and start the progressed-disease regimen. Hypothetically, a patient could progress one day after that CT-scan, remain treated as if he were metastasis-free for the following 16 weeks and only be considered as progressed after the CT-scan after 16 weeks. While this CEA mimics the biological process better, it does not fully comply with the protocol, while this protocol is what happens in real-life and what decides the treatment regimen and thus costs. This would mean that the costs and life-years for MF-state in the model could be underestimated and the costs and life-years in the PD-state overestimated. When only considering the costs, this could lead to an (large) increase of the ICER, when observing the scenario analyses. Nevertheless, if it was possible to model this way, life-years in MF-state would increase in proportion as well, this effect could become balanced. There is not definite answer to this hypothesis unfortunately. Secondly, several SEs had to be estimated with percentages for the PrSA. The higher the uncertainty surrounding those values, the higher the percentage for that specific SEs. As Briggs et al. mentions, this is not a complete guess (20). However, it is not based on verifiable data and can thus be considered a limitation.

Even with all these limitations in mind, it is still highly unlikely that the treatment of nonmetastatic castration-resistant prostate cancer with apalutamide plus androgen deprivation therapy will be cost-effective. This is in line with some of the previously mentioned literature, such as Parmar et al. (13). On the contrary, the result of this CEA was slightly surprising when observing the other literary sources. Bin Riaz et al. concluded that apalutamide was cost-effective based on the US-threshold (14). Since the US has quite a different threshold and since that cannot be compared directly to the ICER that has been calculated in this CEA, another finding in that article might be even more significant. They concluded that apalutamide + ADT is more cost-effective than enzalutamide + ADT. NICE has already conducted a CEA for enzalutamide + ADT and found that this treatment regimen is cost-effective. The population of this CEA was nmCRPC as well (17). In line with expectations, it is presumed that apalutamide would be even ‘more’ cost-effective. ICERs from different CEAs cannot be compared directly. However, the costs for 112 tablets of enzalutamide are £2734.67 according to the BNF, which is very close to the costs of apalutamide (37). It is interesting to find out what caused the significant difference between those ICERs. The hypothesis is that the

post-progression treatment chosen in the NICE-CEA differs from that of this CEA as an increase in PD-costs, causes a decreased (deterministic) ICER.

Following these observations and acknowledging that CEAs cannot be compared directly, it would be very interesting to construct a Markov model in which enzalutamide and apalutamide are compared to each other. This has been conducted before from a US-perspective, but this cannot be directly applied to the UK (14). Alternatively, another CEA of apalutamide can be conducted but with the exact same post-progression care as has been applied in the enzalutamide-CEA. Another suggestion for further research would be to investigate the cost-effectiveness in different disease stages, such as metastatic or hormone sensitive PCa. The second proposition seems the most promising, considering the fact that the main aim of apalutamide is to prolong MFS. Furthermore, as has been mentioned by Bin Riaz, doralutamide has the highest tolerability of the three drugs (14). It might be interesting to see if the loss of effectiveness is made up for by a decrease in AEs. Since the effect of AEs in this CEA was only moderate, the hypothesis is that this will not be the case. Another robust and ethically ambiguous research subject is to investigate the cost-effectiveness on a younger patient population. The median age in the apalutamide group was 74-years-old and most patients that receive the diagnosis PCa are 65+-years-old (1,8). Nonetheless, this does not mean that there are no younger patients receiving this diagnosis. It would be interesting to see if the clinical effects are even greater in this group and if that is the case, what way this would impact the cost-effectiveness.

Aside from the outcome of this analysis, some ethical considerations must be kept in mind. A small but not insignificant detail about the SPARTAN-trial, is that there are seven patients who died because of adverse events in the apalutamide group and one in the placebo group. In total, only two individuals died of PCa during the trial. Of course, these risks are all incorporated within the model and the EMA and Food and Drug Administration (FDA) approved apalutamide. Nevertheless, as some people critique CEAs for its attribute to lose sight of the individual patient, it was deemed noteworthy to mention.

On top of that, contrary to a cost-benefit analysis, a CUA as the one in this thesis, addresses the fact that it is important to consider quality of life. But still, many people view these types of analyses as being barbaric because a monetary value is placed on human-life (46). They find the way in which the economic principles are prioritized unacceptable and critique the inability to incorporate societal values such as respect for old age and joyous youth in these analyses (46). This way of healthcare budget allocation is considered unfair. However, this seems to be the directly opposite to what a CEA is meant to accomplish. While health care resources are inevitably scarce and clinicians have to make tough decisions on a daily basis, a rational way of allocations seems harsh but is

necessary to make decisions that cannot be taken for individual patients. Not limiting healthcare costs would eventually lead to less access and more inequity and inequality in healthcare. This, understandably, could feel counterinitiative to some people. Of course, some things could be enhanced about CEAs in general. For example, QALYs of children could way heavier or those CEAs could have a higher WTP-threshold. This way, societies preferences can be incorporated in this cost-effectiveness analysis type of decision-making, according to Pinkerton et al. (46).

To conclude, the cost-effectiveness of apalutamide plus androgen deprivation therapy as treatment for nonmetastatic, castration-resistant prostate cancer compared to androgen deprivation therapy plus placebo for adult men in the UK, is £101.854 per QALY. According to the willingness to pay threshold in the UK, this is not considered cost-effective.

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## 7. Appendices

**Appendix 1: all input parameters used in the Markov model**

| *Parameter* | *Deterministic value* | *Standard error* | *Distribution* | *Alpha* | *Beta* |
|---|---|---|---|---|---|
| *Utility of stable disease state (progression free) of apalutamide group* | 0,7620 | 0,169 | Beta | 4,077 | 1,273 |
| *Utility of stable disease state (progression free) of placebo group* | 0,7680 | 0,169 | Beta | 4,023 | 1,215 |
| *Utility of progressed disease state (metastasised) of both groups* | 0,7170 | 0,1434 | Beta | 6,358 | 2,510 |
| *Utility of death state* | 0,0000 | | None | | |
| *Disutility of fatigue* | 0,0940 | 0,0163 | Beta | 30,037 | 289,502 |
| *Disutility of diarrhoea* | 0,0470 | 0,0082 | Beta | 31,261 | 633,875 |
| *Disutility of nausea* | 0,2100 | 0,02 | Beta | 86,888 | 326,863 |
| *Disutility of rash* | 0,0325 | 0,01171 | Beta | 7,411 | 220,761 |
| *Disutility of hypertension* | 0,1530 | 0,0306 | Beta | 21,022 | 116,377 |
| *Disutility of weight loss* | 0,0020 | 0,0004 | Beta | 24,948 | 12449,052 |
| *Disutility of arthralgia* | 0,0690 | 0,0138 | Beta | 23,206 | 313,113 |
| *Disutility of falls* | 0,0690 | 0,0138 | Beta | 23,206 | 313,113 |
| *Disutility of pathological fracture* | 0,2010 | 0,0402 | Beta | 19,774 | 78,604 |
| *Disutility of dizziness* | 0,1250 | 0,0217 | Beta | 28,909 | 202,364 |
| *Disutility of hypothyroidism* | 0,1000 | 0,02 | Beta | 22,400 | 201,600 |
| *Disutility of mental-impairment disorders* | 0,0600 | 0,012 | Beta | 23,440 | 367,227 |
| *Disutility of seizure* | 0,0600 | 0,012 | Beta | 23,440 | 367,227 |
| *Duration of fatigue in days* | 91,2500 | 18,25 | Gamma | 25,000 | 3,650 |
| *Duration of diarrhoea in days* | 8,0000 | 1,6 | Gamma | 25,000 | 0,320 |

| | | | | | |
|---|---|---|---|---|---|
| *Duration of nausea in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Duration of rash in days* | 60,0000 | 3 | Gamma | 400,000 | 0,150 |
| *Duration of hypertension in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Duration of weight loss in days* | 90,0000 | 18 | Gamma | 25,000 | 3,600 |
| *Duration of arthralgia in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Duration of falls in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Duration of fracture in days* | 30,4200 | 6,084 | Gamma | 25,000 | 1,217 |
| *Duration of dizziness in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Duration of hypothyroidism in days* | 113,0000 | 5,65 | Gamma | 400,000 | 0,283 |
| *Duration of mental-impairment disorders in days* | 90,0000 | 18 | Gamma | 25,000 | 3,600 |
| *Duration of seizure in days* | 10,5000 | 2,1 | Gamma | 25,000 | 0,420 |
| *Probability of experiencing fatigue in apalutamide group* | 0,0090 | 0,003326523 | Beta | 7,254 | 798,746 |
| *Probability of experiencing fatigue in placebo group* | 0,0030 | 0,00273109 | Beta | 1,203 | 399,797 |
| *Probability of experiencing diarrhoea in apalutamide group* | 0,0100 | 0,003504694 | Beta | 8,060 | 797,940 |
| *Probability of experiencing diarrhoea in placebo group* | 0,0050 | 0,003522284 | Beta | 2,005 | 398,995 |
| *Probability of experiencing nausea in apalutamide group* | 0,0000 | | None | | |
| *Probability of experiencing nausea in placebo group* | 0,0000 | | None | | |
| *Probability of experiencing rash in apalutamide group* | 0,0520 | 0,007820568 | Beta | 41,912 | 764,088 |
| *Probability of experiencing rash in placebo group* | 0,0030 | 0,00273109 | Beta | 1,203 | 399,797 |

| | | | | | |
|---|---|---|---|---|---|
| *Probability of experiencing hypertension in apalutamide group* | 0,1430 | 0,01233079 | Beta | 115,258 | 690,742 |
| *Probability of experiencing hypertension in placebo group* | 0,1180 | 0,016110281 | Beta | 47,318 | 353,682 |
| *Probability of experiencing weight loss in apalutamide group* | 0,0110 | 0,003673897 | Beta | 8,866 | 797,134 |
| *Probability of experiencing weight loss in placebo group* | 0,0030 | 0,00273109 | Beta | 1,203 | 399,797 |
| *Probability of experiencing arthralgia in apalutamide group* | 0,0000 | | None | | |
| *Probability of experiencing arthralgia in placebo group* | 0,0000 | | None | | |
| *Probability of experiencing falls in apalutamide group* | 0,0170 | 0,004553378 | Beta | 13,702 | 792,298 |
| *Probability of experiencing falls in placebo group* | 0,0080 | 0,004448654 | Beta | 3,208 | 397,792 |
| *Probability of experiencing pathological fracture in apalutamide group* | 0,0270 | 0,005709141 | Beta | 21,762 | 784,238 |
| *Probability of experiencing pathological fracture in placebo group* | 0,0080 | 0,004448654 | Beta | 3,208 | 397,792 |
| *Probability of experiencing dizziness in apalutamide group* | 0,0060 | 0,002720203 | Beta | 4,836 | 801,164 |
| *Probability of experiencing dizziness in placebo group* | 0,0000 | | None | | |
| *Probability of experiencing hypothyroidism in apalutamide group* | 0,0810 | 0,009610207 | Beta | 65,286 | 740,714 |
| *Probability of experiencing hypothyroidism in placebo group* | 0,0200 | 0,006991266 | Beta | 8,020 | 392,980 |

| | | | | | |
|---|---|---|---|---|---|
| *Probability of experiencing mental-impairment disorder in apalutamide group* | 0,0510 | 0,007749089 | Beta | 41,106 | 764,894 |
| *Probability of experiencing mental-impairment disorder in placebo group* | 0,0300 | 0,008518719 | Beta | 12,030 | 388,970 |
| *Probability of experiencing seizure in apalutamide group* | 0,0020 | 0,001573667 | Beta | 1,612 | 804,388 |
| *Probability of experiencing seizure in placebo group* | 0,0000 | | | | |
| *Costs package bicalutamide 150mg* | 5,0700 | 0,013753831 | Gamma | 135884,079 | 0,000 |
| *Costs package apalutamide 60mg* | 2735,0000 | 136,75 | Gamma | 400,000 | 6,838 |
| *Costs package GnRH analogue 3.75mg* | 75,2400 | 7,524 | Gamma | 100,000 | 0,752 |
| *Costs package abiraterone acetate 500 mg* | 2735,0000 | 273,5 | Gamma | 100,000 | 27,350 |
| *Costs package prednisone 5mg* | 0,4000 | 0,000144478 | Gamma | 7665090,539 | 0,000 |
| *Size of bicalutamide package* | 28,0000 | | None | | |
| *Size of apalutamide package* | 112,0000 | | None | | |
| *Size of GnRH analogue package* | 3,0000 | | None | | |
| *Size of abiraterone acetate package* | 56,0000 | | None | | |
| *Size of prednisone package* | 28,0000 | | None | | |
| *Costs haematology examination* | 3,0000 | 0,15 | Gamma | 400,000 | 0,008 |
| *Costs blood chemistry test* | 1,0000 | 0,05 | Gamma | 400,000 | 0,003 |
| *Costs PSA measurement* | 1,0000 | 0,05 | Gamma | 400,000 | 0,003 |
| *Costs testosterone measurement* | 1,0000 | 0,05 | Gamma | 400,000 | 0,003 |
| *Costs thyroid stimulating hormone (TSH) measurement* | 1,0000 | 0,05 | Gamma | 400,000 | 0,003 |
| *Costs fasting lipid panel test* | 6,0000 | 0,3 | Gamma | 400,000 | 0,015 |
| *Costs urinalysis* | 1,0000 | 0,05 | Gamma | 400,000 | 0,003 |
| *Costs ECG 12 lead* | 76,0000 | 3,8 | Gamma | 400,000 | 0,190 |

| | | | | | |
|---|---|---|---|---|---|
| *Costs computer tomography (CT) of 4 areas: brain, abdomen, chest and pelvis* | 111,0000 | 11,1 | Gamma | 100,000 | 1,110 |
| *Costs CT of 3 areas: abdomen, chest and pelvis* | 115,0000 | 11,5 | Gamma | 100,000 | 1,150 |
| *Costs bone scan* | 264,0000 | 13,2 | Gamma | 400,000 | 0,660 |
| *Costs pharmacokinetics (PK) test* | 2,0000 | 0,1 | Gamma | 400,000 | 0,005 |
| *Costs physical exam before cycle 1 day 1, including ECOG and vital signs* | 186,0000 | 37,2 | Gamma | 25,000 | 7,440 |
| *Costs physical exam during treatment* | 104,9000 | 20,98 | Gamma | 25,000 | 4,196 |
| *Costs treatment adverse event fatigue* | 354,0000 | 70,8 | Gamma | 25,000 | 14,160 |
| *Costs treatment adverse event diarrhoea* | 400,0000 | 80 | Gamma | 25,000 | 16,000 |
| *Costs treatment adverse event nausea* | 0,0000 | | Gamma | | |
| *Costs treatment adverse event rash* | 0,3500 | 0,07 | Gamma | 25,000 | 0,014 |
| *Costs treatment adverse event hypertension* | 1849,0000 | 369,8 | Gamma | 25,000 | 73,960 |
| *Costs treatment adverse event weight loss* | 0,0000 | | None | | |
| *Costs treatment adverse event arthralgia* | 269,0000 | 53,8 | Gamma | 25,000 | 10,760 |
| *Costs treatment adverse event falls* | 269,0000 | 53,8 | Gamma | 25,000 | 10,760 |
| *Costs treatment adverse event pathological fractures* | 1841,7300 | 368,346 | Gamma | 25,000 | 73,669 |
| *Costs treatment adverse event dizziness* | 279,7400 | 55,948 | Gamma | 25,000 | 11,190 |
| *Costs treatment adverse event hypothyroidism* | 919,8200 | 183,964 | Gamma | 25,000 | 36,793 |
| *Costs treatment adverse event mental-impairment disorder* | 0,0000 | | None | | |

| | | | | | |
|---|---|---|---|---|---|
| *Costs treatment adverse event seizure* | 968,3800 | 193,676 | Gamma | 25,000 | 38,735 |
| *Costs end-of-life treatment: estimated costs in the last twelve months of life* | 5929,5000 | 1185,9 | Gamma | 25,000 | 237,180 |
| *NHSCII indexing costs year 2019/2020* | 0,0162 | | None | | |
| *Days in a year* | 365,0000 | | None | | |
| *Days in once cycle, cycle length of 28 days* | 28,0000 | | None | | |
| *Number of patients included in the apalutamide arm of SPARTAN-trial* | 806,0000 | | None | | |
| *Number of patients included in the placebo arm of SPARTAN-trial* | 401,0000 | | None | | |

**Appendix 2: disutilities regardless of grade, their median duration and probabilities**

| ***AE grades 3 or 4/special interest*** | ***Apalutamide (any grade)*** | ***Placebo (any grade)*** | ***Disutility, SE (source)*** | ***Duration (source)*** |
|---|---|---|---|---|
| **Fatigue** | 0.9% (30.4%) | 0.3% (21.1%) | -0.094, 0.0163 (26) | 91.25 days (17) |
| **Diarrhoea** | 1% (20.3%) | 0.5% (15.1%) | -0.047, 0.0082 (26) | 8 days (26) |
| **Nausea** | (18.1%) | (15.8%) | -0.21, 0.1171 (47) | 10.5 days (17) |
| **Rash** | 5.2% (23.8%) | 0.3% (5.5%) | -0.03248, 0.01171 (28) | 60 days (25) |
| **Hypertension** | 14.3% (24.8%) | 11.8% (19.8%) | -0.153 (17) | 10.5 days (17) |
| **Weight loss** | 1.1% (16.1%) | 0.3% (6.3%) | -0.002 (29) | 90 days (27) |
| **Arthralgia** | (15.9%) | (7.5%) | -0.069 (27) | 10.5 days (17) |
| **Falls** | 1.7% (15.6%) | 0.8% (9.0%) | -0.069 (17) | 10.5 days (17) |
| **Pathological fracture** | 2.7% (11.7%) | 0.8% (6.5%) | -0.201 (17) | 30.42 days (17) |
| **Dizziness** | 0.6% (9.3%) | (6.3%) | -0.125, 0.0217 (26) | 10.5 days (17) |
| **Hypothyroidism** | 8.1% | 2.0% | -0.1 (31) | 113 days (31) |

| | | | | |
|---|---|---|---|---|
| **Mental-impairment disorder** | 5.1% | 3.0% | -0.06 (30) | 90 days (27) |
| **Seizure** | 0.2% | 0% | -0.06 (30) | 10.5 days (27) |

**Appendix 3: drug acquisition costs with dosage**

| **Apalutamide - MFS** | | | **Placebo - MFS** | | |
|---|---|---|---|---|---|
| ***Drug and dosage*** | *Costs* | *Source* | *Drug* | *Costs* | *Source* |
| *ADT (bicalutamide) (150mg/day, 1x 150mg tablet orally)* | £5.07/28 tablets | (36) | ADT (bicalutamide) (150mg/day, 1x 150mg tablet orally) | £5.07/28 tablets | (36) |
| *Apalutamide (240mg/day, 4x 60mg tablet orally)* | £2735.00/ 112 tablets | (37) | | | |
| *GnRH analogue (Lucrin) (1x 1mg (0,2 ml) injection)* | £75.24/3.75mg | (37)) | GnRH analogue (29, 31) (Lucrin) (1x 1mg (0,2 ml) injection) | £75.24/3.75mg | (37) |
| **Metastasised – Apalutamide and placebo** | | | | | |
| ***Drug and dosage*** | *Costs* | *Source* | | | |
| *Abiraterone acetate (1000mg/day, 2x 500mg tablet orally)* | £2735/56 tablets | (37) | | | |
| *Prednisone (30) (10 mg/day, 2x 5mg tablet orally)* | £0,40/28 tablets | (36) | | | |
| *GnRH analogue (29, 31) (Lucrin) (1x 1mg (0,2 ml) injection)* | £75.24/3.75mg | (37) | | | |

**Appendix 4: schedule of all health care resource used during MF and PD**

| **Activity** | Screening | Day 1 cycle 1 | Day 1 every other cycle | Post-progression |
|---|---|---|---|---|
| *Physical examination (extended), including ECOG, body weight, vital signs* | x | | | |
| *Physical examination (routine) including ECOG, body weight, vital signs* | | x | x | x |
| *Haematology* | x | x | x | x |
| *Blood chemistry* | x | x | x | x |
| *PSA* | x | x | x | x |
| *Testosterone* | x | | Every 16 weeks | |
| *Thyroid stimulating hormone (TSH)* | x | | Every 16 weeks | |
| *Fasting Lipid Panel* | x | | Every 16 weeks | |
| *Urinalysis* | x | | Every 16 weeks | |
| *12-lead ECG* | x | | | |
| *CT-brain* | x | | | |
| *CT-chest, -abdomen, - pelvis* | x | | Every 16 weeks | x |
| *Bone scan* | x | | Every 16 weeks | x |
| *Pharmacokinetic sample (plasma samples)* | | x | Cycle 2, 3, 6, 12, 18, 24 and 36 and yearly after* | x |

***** The model starts with cycle 0, while the first cycle in Smith et al. is cycle 1 (23). The abovementioned cycles are thus applied on cycle 1, 2, 5, 11, 17, 13 and 35 in the model.

**Appendix 5: HCRU-costs**

| Activity | Costs | Source |
|---|---|---|
| *Physical examination (extended), including ECOG, body weight, vital signs* | £186 | (39) |
| *Physical examination (routine), including ECOG, body weight, vital signs* | £104,90 | (39) |
| *Haematology* | £3 | (39) |
| *Blood chemistry* | £1 | (39) |
| *PSA* | £1 | (39) |
| *Testosterone* | £1 | (39) |
| *TSH* | £1 | (39) |
| *Fasting Lipid Panel* | £6 | (39) |
| *Urinalysis* | £1 | (39) |
| *12-lead ECG* | £76 | (39) |
| *CT-brain, -chest, -abdomen, - pelvis* | £111 | (39) |
| *CT-chest, -abdomen, - pelvis* | £115 | (39) |
| *Bone scan* | £264 | (39) |
| *Pharmacokinetic sample (plasma samples)* | £2 | (39) |

**Appendix 6: R-output**

| ***OS for apalutamide*** | | | | |
|---|---|---|---|---|
| | exponential | Weibull | lognormal | loglogistic |
| **AIC** | 2768.99580250184 | 2631.91385659606 | 2632.74379913479 | 2630.29320329682 |
| **intercept** | 4.87477754010694 | 4.36430915570384 | 4.26766172196093 | 4.21983126982345 |
| **log(scale)** | | -0.745092705973049 | -0.232967645121622 | -0.862304234833245 |
| ***OS for placebo*** | | | | |
| | exponential | Weibull | lognormal | loglogistic |
| **AIC** | *1555.78051149994* | *1484.44407939418* | *1483.50195231431* | *1481.01531969706* |
| **intercept** | *4.6414772590285* | *4.25529493158568* | *4.10853872227778* | *4.07690884633818* |
| **log(scale)** | | *-0.685128203037365* | *-0.228091796369228* | *-0.838871571050205* |
| ***MFS for apalutamide*** | | | | |
| | exponential | Weibull | lognormal | loglogistic |
| **AIC** | 1909.89 | 1874.627 | 1869.353 | 1872.51 |
| **intercept** | 4.299686 | 3.859903 | 3.77727 | 3.67606 |
| **log(scale)** | | -0.4223907 | 0.12544 | *-0.5219777* |
| ***MFS for placebo*** | | | | |
| | exponential | Weibull | lognormal | loglogistic |
| **AIC** | 1545.286 | 1532.478 | 1504.356 | 1520.017 |
| **intercept** | 3.193641 | 3.087683 | 2.739526 | 2.736229 |
| **log(scale)** | | -0.243421 | 0.04334159 | -0.464594 |

**Appendix 7: deterministic disaggregated results**

| | Apalutamide + ADT | Placebo + ADT | Increment |
|---|---|---|---|
| ***Drug acquisition costs MFS*** | £ 159.459,86 | £15.578,80 | *£143.881,06* |
| ***HCRU-costs MFS*** | £10.037,49 | £5.268,90 | *£4.768,59* |
| ***AE costs MFS*** | £1.988,77 | £1.887,46 | *£101,30* |
| ***Drug acquisition costs PD*** | £99.990,94 | £156.925,18 | *-£56.934,24* |
| ***HCRU-costs PD*** | £14.776,19 | £23.189,67 | *-£8.413,48* |
| ***EoL-costs*** | £5.929,50 | £5.929,50 | *£0,00* |
| | | | |
| ***QALYs accrued in MFS*** | 2.72 | 1.30 | *1.41* |
| ***QALYs accrued in PD state*** | 1.60 | 2.70 | *-1.09* |
| ***QALYs lost due to adverse events*** | 0.00 | 0.00 | *0.00* |
| ***Lys accrued in MFS*** | 3.56 | 1.69 | *1.87* |
| ***LYs accrued in PD state*** | 2.24 | 3.51 | *-1.27* |