NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Antiandrogen Therapies for non-metastatic Castration-Resistant Prostate Cancer

Modeling Analysis Plan

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1. Overview

This document presents the analysis plan that details our modeling approach and outcomes to be assessed for the economic evaluation of antiandrogen therapies for non-metastatic castration-resistant prostate cancer (nmCRPC). Refer to the protocol for details on the systematic review of the clinical evidence on this topic.

2. Approach

The primary aim of this analysis will be to estimate the lifetime cost-effectiveness of antiandrogen therapies as first line treatment of nmCRPC, from a U.S. payer perspective. The model will include (1) apalutamide (Erleada™; Janssen Biotech, Inc.), (2) enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.); and potentially (3) abiraterone acetate (Zytiga®; Janssen Biotech, Inc.) + prednisone as a scenario analysis, if data allow. The base case/standard of care comparison will be continued androgen deprivation therapy (ADT). Patient survival, quality-adjusted survival, and health care costs will be summarized over a lifetime time horizon for each treatment option. The analytic framework for this assessment is depicted in Figure 1 below. The model will be developed in Microsoft Excel (Redmond, WA).

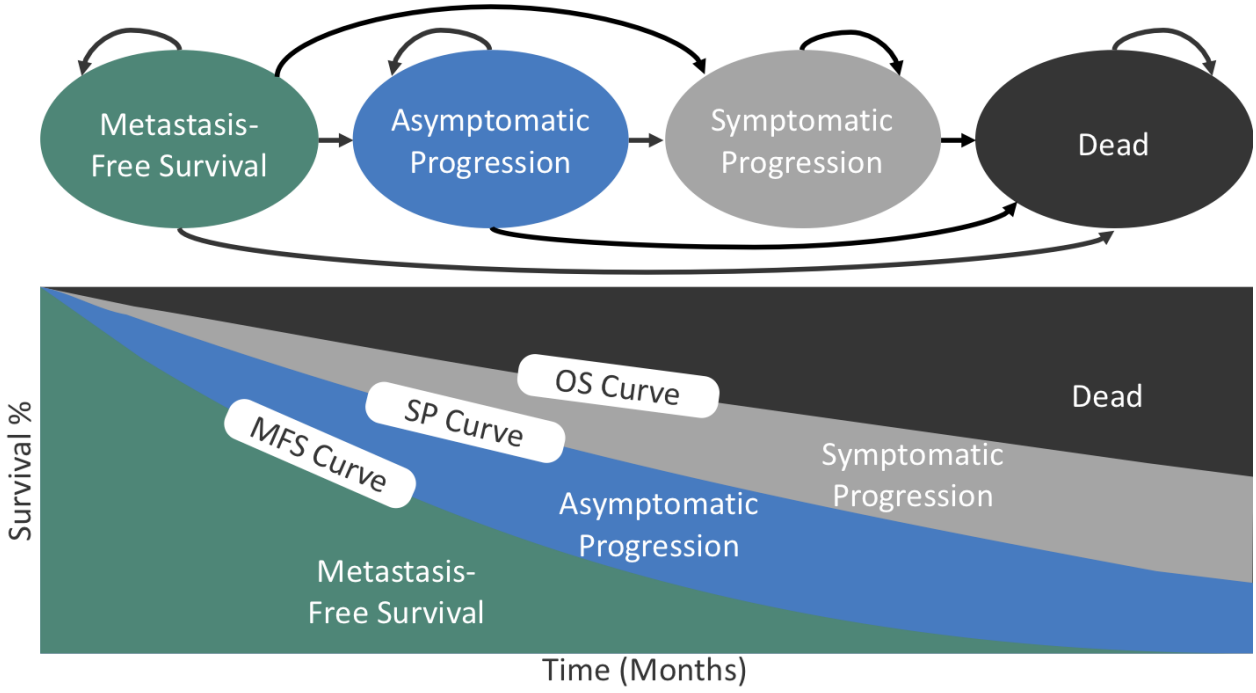
3. Methods

3.1 Model Structure

We will develop a *de novo* decision analytic model including four health states: metastasis-free survival, asymptomatic progression, symptomatic progression, and death (Figure 1). Health states and transitions among them will be modeled using a partitioned survival approach, a type of economic model used to follow a hypothetical cohort of patients through time as they move among a set of mutually exclusive heath states. The partitioned model estimates the proportion of a cohort in each health state for each model cycle based on the difference in parametric survival curves, in this case those for metastasis-free survival, time to symptomatic progression, and overall survival.[1]

For each treatment regimen, a hypothetical nmCRPC patient population will begin the model in the metastasis-free survival health state, where they remain until they either: (a) experience metastasis/disease progression or (b) die from cancer or other causes. Patients who experience metastasis/progression may either be asymptomatic or symptomatic; asymptomatic patients can become symptomatic but symptomatic patients cannot return to asymptomatic progression. All patients can transition to death from any of the alive health states.

Figure 1. Model Framework



3.2 Treatments

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of antiandrogen interventions considered for the model is as follows:

- Apalutamide (Erleada™; Janssen Biotech, Inc.)
- Enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.)
- Abiraterone acetate (Zytiga®; Janssen Biotech, Inc.) + prednisone (as a scenario analysis, if data allow)

- Universal base case comparator: continued ADT without antiandrogen therapy

3.3 Target Population

The population of focus for this review is men diagnosed with nmCRPC. If data permit, we will examine subgroups based on rate of doubling of PSA levels, including those with doubling times greater than 10 months (based on published trial cutoffs[2]), and extent of disease at baseline.

Table 1. Clinical Trial Population Characteristics

Patient population	Median Age	Median Weight*	Median Height*	Median Diagnosis to Randomization Time	Median PSA Doubling Time
Apalutamide[2]	74 years	85.0 kg	172 cm	7.95 months	4.40 months
Enzalutamide[3]	74 years	Not reported	Not reported	Not reported	77% had PSA doubling time <6 months
Continued ADT[2,3]	74 years	83.2 kg	173 cm	7.85 months	4.50 months

*Used to calculate dosage of docetaxel for subsequent treatment cost. The median weight for all patients combined in SPARTAN was 84.4 kg, and the median combined height was 173 cm.

3.4 Key Model Choices and Assumptions

- Model cycle length will be one month (365.25/12 = 30.44 days/month) since each comparator is a daily oral drug, which precludes the need for a shorter cycle length to capture complex/irregular regimen schedules and drug administration fees. Furthermore, monthly model cycles reflect the unit of measurement for nmCRPC survival in clinical trials.[2-4]
- Parametric curve functions will be fit separately for each survival curve available in the published literature, and used to extrapolate the data to a lifetime horizon. For the main analysis, available curves include those for apalutamide (metastasis-free survival, time to symptomatic progression, and overall survival)[2]; enzalutamide (metastasis-free survival)[3]; and continued ADT (metastasis-free survival [SPARTAN and PROSPER trials], time to symptomatic progression [SPARTAN only], and overall survival [SPARTAN only]).[2,3]
- Estimates of time to symptomatic progression and overall survival for enzalutamide are currently unavailable. We will utilize available information from the PROSPER trial[3] and the observed differences between apalutamide and continued ADT from the SPARTAN trial[2] to derive calibrated survival estimates for time to symptomatic progression and overall survival for enzalutamide.
- Survival will be weighted by health state utilities to model quality of life. The model will include separate utilities for metastasis-free survival, asymptomatic progression, and symptomatic progression.
- The model will include costs and, if available, (dis)utilities for individual grade 3/4 adverse events that occur in at least 5% of patients in at least one of the included regimens.
- Grade 2 fractures will be included as these are considered of specific relevance to patients, provided there are data showing their impact on quality of life and costs.
- The model will include all treatment costs associated with each individual regimen, including drug acquisition costs, supportive care costs, and costs of disease metastasis/progression.
- Disease metastasis/progression costs will reflect a distribution of subsequent treatments and best supportive care. The cost per month in disease metastasis/progression will be consistent across comparators.
- All survival and health care costs will be discounted at 3% per year.[5]

Table 2. Key Model Assumptions

Assumption	Rationale
Treatment effects as represented by the parametric survival functions based on available Kaplan-Meier data and/or hazard ratios from SPARTAN[2] and PROSPER[3] trials is consistent throughout long-term extrapolation.	In the absence of long-term follow-up data, a consistent approach in survival extrapolations is recommended for the base case analysis. Scenario analyses, for example using a response-based landmark model or a parametric mixture model, may be performed if data allow.
Trial populations were sufficiently homogeneous to allow for comparisons to a single baseline comparator (continued ADT from the SPARTAN trial[2]). A scenario analysis using the metastasis-free survival curve from the PROSPER trial[3] will also be explored.	Review of reported patient characteristics across clinical trials were similar, and metastasis-free survival for the continued ADT arm in the SPARTAN and PROSPER trials were similar.
Treatment received after progression is informed by subsequent approved treatments for metastatic CRPC in the SPARTAN trial.	Detailed information on post-progression therapy not available or not provided for all regimens of interest.
Time to symptomatic progression and overall survival are similar between apalutamide and enzalutamide.	These two enzalutamide outcomes are currently unknown from available trial results and are needed to fully analyze enzalutamide within the chosen model framework. Metastasis-free survival outcomes for apalutamide[2] and enzalutamide[3] are very similar, leading to the assumption that secondary outcomes are also similar.
Patients on each antiandrogen treatment are assumed to continue to be treated with ADT until death.	Continued ADT is the standard of care for metastatic CRPC.

3.5 Input Parameters

Systematic review

Refer to the protocol for details on the systematic review of the clinical evidence on this topic.

Table 3. Results of Systematic Review

Hazard Ratios vs. baseline comparator (continued ADT)	Metastasis-Free Survival	Time to Symptomatic Progression	Overall Survival
Apalutamide	0.28 (95% CI, 0.23–0.35)	0.45 (95% CI, 0.32–0.63)	0.70 (95% CI, 0.47–1.04)
Enzalutamide	0.29 (95% CI, 0.24–0.35)	NA*	NA*

*Estimates not currently available. Enzalutamide time to symptomatic progression and overall survival will be derived based on outcomes for apalutamide vs. continued ADT and model calibration.

Survival Modeling

We will fit parametric survival curves to (1) metastasis-free survival, (2) time to symptomatic progression, and (3) overall survival Kaplan-Meier data for the standard of care (continued ADT) and apalutamide arms of the SPARTAN trial and metastasis-free survival Kaplan-Meier data for the enzalutamide arm of the PROSPER trial utilizing the approach described by Hoyle and Henley.[6] This approach will allow us to model the relative efficacy of the interventions, model survival beyond available follow-up time, and facilitate probabilistic sensitivity analysis of survival. First we will extract data points from digitized copies of the SPARTAN trial[2] curves, then use the extracted values, the number of remaining patients at each time interval, and maximum likelihood functions to estimate curve fits to the underlying individual patient data. The model curves will include the distributional forms Weibull, exponential, log-normal, log-logistic, gamma, and Gompertz. The base case parametric functions for each comparator will be selected based on best model fit using Akaike information criterion (AIC) values, Bayesian information criterion (BIC) values, and visual comparison. For survival curves for which Kaplan-Meier data are unavailable, we will utilize available information from the PROSPER trial[3] and the observed survival differences between apalutamide and continued ADT from the SPARTAN trial[2] to derive calibrated survival curves.

Lastly, for each comparator, the lesser of the following survival curve hierarchy will be modeled at each time point to prevent curves from "crossing":

- Overall survival curve: Minimum of U.S. life table[7] survival and overall survival.
    - Symptomatic progression curve : Minimum of overall survival and time to symptomatic progression.
        - Metastasis-free survival curve: Minimum of time to symptomatic progression and metastasis-free survival.

Drug utilization

The estimation of drug utilization will be derived from several factors, including the relative dose intensity and dosing schedule reported in trials (Table 4). Each regimen is administered until metastasis/progression; thus the treatment utilization and cost will be applied to all patients who remain in the metastasis-free survival health state over time. Treatment regimen post-progression

is based on that seen in the SPARTAN trial. Drug unit costs (see Table 5) will be applied to the utilization estimates to calculate total estimated treatment costs.

Table 4a. Treatment Regimen Recommended Dosage, Antiandrogen Therapies

	Apalutamide	Enzalutamide	Abiraterone acetate + prednisone‡
Brand name	Erleada®	Xtandi®	Zytiga®
Manufacturer	Janssen	Astellas & Pfizer	Janssen
Route of administration	Oral	Oral	Oral
Dosage Forms and Strengths	Tablets: 60 mg	Capsules: 40 mg	Tablets: 250 mg
Recommended Dosing	240 mg (four 60 mg tablets) administered orally once daily	160 mg (four 40 mg capsules) administered orally once daily*	1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily*

‡For scenario analysis

*Enzalutamide and abiraterone acetate are currently not indicated for nmCRPC. The listed recommend dosing is that for metastatic CRPC.

Table 4b. Treatment Regimen Recommended Dosage, Continued ADT

	Leuprolide Acetate	Goserelin Acetate	Triptorelin Pamoate	Degarelix Acetate
Brand name	Eligard®	Zoladex®	Trelstar®	Firmagon®
Manufacturer	Tolmar Pharmaceuticals	TerSera Therapeutics	Allergan	Ferring Pharmaceuticals
Route of administration	Subcutaneous injection	Subcutaneous injection	Intramuscular injection in either buttock	Subcutaneous injection
Dosage Forms, Strengths, & Recommended Dosing	• 7.5 mg subcutaneously every month • 22.5 mg subcutaneously every 3 months • 30 mg subcutaneously every 4 months • 45 mg subcutaneously every 6 months	3.6 mg subcutaneously every 28 days	• 3.75 mg every 4 weeks • 11.25 mg every 12 weeks • 22.5 mg every 24 weeks	• Starting dose of 240 mg given as two injections of 120 mg each‡ • Maintenance doses of 80 mg administered as a single injection every 28 days

‡Starting/loading dose is not included in the model since patients are assumed to enter the model having previously started ADT.

Drug Cost Inputs

For enzalutamide and abiraterone acetate, we obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price. We estimated net prices by comparing the four-quarter averages (i.e., first quarter of 2017 through fourth quarter of 2017) of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (May 16th, 2018) to arrive at an estimated net price per unit. Because apalutamide was only recently approved by the FDA, we do not have any estimates on its discount from WAC, so we assumed a 30% discount which was in line with the discount off WAC for the other two anti-androgen therapies. We then applied this discount to apalutamide's current WAC to arrive at its assumed net price. For prednisone, since multiple inexpensive generic options are available, we used the WAC and not net price. For all ADTs except Triptorelin pamoate, the net price has been derived using the drug price listed in the May 2018 Federal Supply Schedule, since no SSR price was available for the three out of four ADTs. Based on the regimen dosage specified above, the model will utilize the lowest cost combination of tablets/vials for each regimen.

Table 5. Drug Costs

	WAC Per Dose	Net Price Per Dose	Discount from WAC	Net Price Per Month	Source
Apalutamide (Erleada®) 60mg	$91	$63.70	30%‡	$7,756.11	Redbook[8]; Assumption
Enzalutamide (Xtandi®) 40mg	$90.88	$64.45	29%	$7,847.62	Redbook[8]; SSR Health[9]
Abiraterone Acetate (Zytiga®) 250mg	$85.27	$58.60	31%	$7,134.79	Redbook[8]; SSR Health[9]
Prednisone 5mg*	$0.52	-	-	$31.66*	Redbook[8]
Leuprolide Acetate (Eligard) - 7.5mg	$451.69	$113.98	75%	$113.98	Redbook[8]; Federal Supply Schedule[10]
Goserelin Acetate (Zoladex) - 3.6mg	$605	$276.8	54%	$300.90	Redbook[8]; Federal Supply Schedule[10]
Triptorelin Pamoate (Trelstar) - 3.75mg	$813.24	$434.06	47%	$471.85	Redbook[8]; SSR Health[9]
Degarelix Acetate (Firmagon) - 80mg	$488.45	$199.34	59%	$216.69	Redbook[8]; Federal Supply Schedule[10]
Docetaxel 1mg	$8.07	-	-	$1,977.60*¶ (BSA = 1.98 mg/m^2)	Redbook[8]

‡Average discount calculated based on discount for enzalutamide and abiraterone acetate

*Average WAC of generics used in place of net price in accordance with ICER's methods of calculating drug costs when multiple generics are available

¶Includes intravenous administration cost ($163.32), from CPT 96413, average reimbursement, non-facility limiting charge, year 2018: Chemo iv infusion 1 hr

BSA = body surface area based on median patient height and weight from SPARTAN.

Healthcare Utilization Inputs

We will estimate a weighted cost of subsequent treatment following metastasis/progression based on the most common subsequent treatment regimens given to patients in the SPARTAN trial.[2] For the apalutamide arm, 314 patients discontinued initial treatment, of which 165 (52.5%) received

subsequent treatment for metastatic CRPC and the remainder received no treatment. For the placebo arm (continued ADT), 279 patients discontinued treatment, of which 161 (77.7%) received subsequent treatment for metastatic CRPC and the remainder received no treatment.[2] The weighted cost of subsequent treatment for enzalutamide patients will be based on the apalutamide arm of SPARTAN, as these estimates are currently unknown.

Apalutamide and continued ADT patients will receive a weighted average cost of abiraterone acetate, enzalutamide, docetaxel, or receive no treatment. Enzalutamide patients will receive a weighted average cost of abiraterone acetate, docetaxel, or receive no treatment, so that subsequent therapy cost does not include the initial therapy of enzalutamide; for this derivation, the reported proportion of enzalutamide received by apalutamide patients in SPARTAN will be added to the proportion of abiraterone acetate. Given that all three subsequent treatment regimens are treat to progression, the weighted cost of subsequent treatment will be based on the monthly cost of each drug plus monthly administration costs for the intravenously administered docetaxel.

Table 6. Post-Progression Treatment Inputs

Proportion Treated → Subsequent Treatment ↓	Cost/Month	Apalutamide [2]	Enzalutamide*	Continued ADT[2]
Abiraterone acetate + prednisone	$7,134.79	125/314 = 40%; WA = 40%	145/314 = 46%; WA = 47%	161/279 = 58%; WA = 60%
Enzalutamide	$7,847.62	20/314 = 6%; WA = 6%	--	28/279 = 10%; WA = 10%
Docetaxel	$1,977.60	15/314 = 5%; WA = 5%	15/314 = 5%; WA = 5%	18/279 = 6%; WA = 7%
No Treatment (continued ADT only)	$220.67‡	149/314 = 47%; WA = 48%	149/314 = 47%; WA = 48%	62/279 = 22%; WA = 23%

WA = weighted average

*Currently unknown, thus subsequent treatment for enzalutamide patients is based on subsequent treatment for apalutamide; the proportion of enzalutamide reported for apalutamide patients in SPARTAN is added to the proportion of abiraterone acetate.

‡Based on distribution of ADT therapies in the SPARTAN trial.

Other healthcare costs will be derived from the published literature. Currently, we will use costs of supportive care and cost of prostate cancer death estimates from a previous cost-effectiveness analysis of localized prostate cancer by Cooperberg et al.,[11] however our review for these estimates is still ongoing. All costs have been inflated to April 2018 dollars, using the Bureau of Labor Statistics, Medical Care component of the Consumer Price Index.

Table 7. Healthcare Utilization and Cost Inputs

	Estimate	Source
Annual MFS Supportive Care	$610	Cooperberg et al.[11] Bureau of Labor Statistics[12]
Annual Metastasis Supportive Care	$2,833	Cooperberg et al.[11] Bureau of Labor Statistics[12]
Prostate Cancer Death (Last Year)	$52,262	Cooperberg et al.[11] Bureau of Labor Statistics[12]

Health State Utilities

Health state utilities will be derived from publicly available literature and/or manufacturer submitted data (if available) and applied to the three alive disease states. The model will use consistent health state utility values across treatments evaluated in the model. The current utility for metastasis-free survival is taken from a Canadian cost-effectiveness analysis of prostate-specific antigen-based screening. We will use asymptomatic and symptomatic progression utilities from Lloyd et al., who report the five-level EuroQol five-dimensional questionnaire (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) to estimate utilities from a total sample of 163 U.K. men with metastatic CRPC.[13] The EQ-5D-5L utilities as stratified by prostate cancer disease states will be used for the model. We will also include utilities related to fractures.[14]

Table 8. Quality of Life Inputs

Parameter	Value	Lower Bound	Upper Bound
Utility: metastasis-free survival[15]	0.900	0.720	0.990
Utility: metastasis/progressed disease: asymptomatic[13]	0.830	0.795	0.865
Utility: metastasis/progressed disease: symptomatic[13]	0.692	0.588	0.796
Utility: Fracture due to cancer treatment, 1st year[14]	0.83	0.664	0.99
Utility: Fracture due to cancer treatment, post 1st year[14]	0.87	0.69	0.99-

Adverse Events

The model will include any common adverse events that occur in >5% of patients as reported in publicly available sources (e.g. the drug's prescribing information), as well as any serious adverse events of interest documented in the trials. Each adverse event will have an associated cost and

disutility that will be applied for each patient experiencing such an event. Costs for adverse events will be based on resource utilization associated with appropriate adverse event treatments as reported in previous analyses and unit prices from the Centers for Medicare and Medicaid Services (CMS) Final Rule and Correction Notice Tables for the fiscal year 2018.[16] for the fiscal year 2018.[16]

Table 9. Adverse Event Inputs

Grade 3-4 Adverse Events and Other Adverse Events of Interest	Adverse Event Cost	Apalutamide[2]	Enzalutamide[3]*	Abiraterone acetate + prednisone*
Grade 3-4 Rash[17]	$15,709	5%	NR	
Grade 3-4 Hypertension[17]	$26,406	14%	NR	
Fracture (MS-DRG 563)[16]	$4,529	12%	NR	
Dizziness (MS-DRG 149) [16]	$3,873	9%	NR	
Hypothyroidism[17]	$1,267	8%	NR	
Mental Impairment Disorder[17]	$2,987	5%	NR	

*Missing values to be determined upon future evidence review.

3.6 Model Analysis

The model will estimate the average amount of time patients spend metastasis-free and in metastasis/progressed disease. Unadjusted and utility-adjusted time spent in each health state will be summed to provide estimates of life expectancy and quality-adjusted life expectancy. We will then calculate incremental cost-effectiveness ratios (ICERs) versus the universal comparator for each intervention. Other model outcomes of interest will be time in asymptomatic and symptomatic progression.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

Multiple scenario analyses will be conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions. As data allow, we will consider conducting the following scenario analyses.

- We will explore a scenario in which overall survival curves will be based on the use of metastasis-free survival as a surrogate outcome, given that (a) nmCRPC patients have an approximately 85% chance of surviving over a 10-year period, and overall survival data from the recent clinical trials is accordingly immature; and (b) metastasis-free survival has been shown to be a strong surrogate for overall survival in localized prostate cancer.[18] Specifically, we will apply the Xie et al. patient-level Kendall's τ correlation coefficient of 0.91 to the modeled metastasis-free survival curves for each comparator to derive each comparator-specific overall survival curve.[18]
- We will explore the impacts of using reported trial hazard ratios applied to the universal comparator survival curves to derive apalutamide, enzalutamide, and abiraterone acetate survival curves, assuming the proportional hazards assumption.
- We will estimate the impacts of using the currently available metastasis-free survival curve for the placebo control in the PROSPER trial as the universal comparator.
- We will consider including abiraterone acetate as an intervention until after the clinical evidence review.
- Finally, we will explore the impact of modeling specific sub-populations from the clinical trials, as data allow.

Model Validation

We will use several approaches to validate the model. First, we will present our methodology and preliminary results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

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