Cost-Effectiveness of Intermittent versus Continuous Androgen Deprivation Therapy in Advanced Prostate Cancer

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Abstract

**Background:** Androgen deprivation therapy (ADT) has known adverse effects (AEs). Intermittent (INT) ADT may reduce AEs, improve quality of life, and lower costs compared to continuous (CONT) ADT. **Objective:** To evaluate the cost-effectiveness of INT vs CONT ADT in men with advanced prostate cancer. **Methods:** A lifetime Markov individual simulation model was developed to evaluate the incremental cost per quality adjusted life month (QALM) of INT vs CONT ADT. **Results:** INT dominated CONT ADT (mean total costs $94,460 vs $109,431; mean total QALMs 47.0 vs 46.4). INT ADT resulted in less time on therapy (22.4 vs 56.8 months), fewer hip fractures (0.080 vs 0.093 per patient), and fewer total cases of sexual dysfunction (72.5% vs 87.0% of patients) and cardiovascular disease (38.7% vs 44.6% of patients). **Conclusions:** These results suggest INT ADT is cost-effective compared to CONT ADT however, differences were small. Additional research is required to confirm these findings.
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List of Abbreviations

ADT = Androgen deprivation therapy
CAB = Combined androgen blockade
CAD = Canadian dollars
CHD = Coronary heart disease
CI = Confidence interval
CVD = Cardiovascular disease
DES = Diethylstilbestrol
ED = Erectile dysfunction
GnRH = Gonadotropin-releasing hormone
HR = Hazard ratio
LHRH = Luteinizing hormone-releasing hormone
MAB = Maximum androgen blockade
MI = Myocardial infarction
NSAA = Non-steroidal anti-androgen
OS = Overall survival
PFS = Progression-free survival
PSA = Prostate specific antigen
QALM = Quality adjusted life month

QALY = Quality adjusted life year

SDF = Sexual dysfunction
1 Introduction

1.1 Statement of the Problem

Prostate cancer is the most commonly diagnosed cancer among men in Canada with an estimated 25,500 new cases in 2011. It is the third leading cause of cancer death among men. Lifetime direct medical costs associated with prostate cancer have been estimated at $9.76 billion ($3.89 billion at 5% annual discount rate) in a Canadian cohort analysis. Prostate cancer is most commonly diagnosed in men aged 60 to 69. Due to the long natural history of the disease, most deaths from prostate cancer occur in men aged 80 and above.

Androgen deprivation therapy (ADT) is the most common form of treatment for men with advanced prostate cancer. The relationship between androgens and prostate cancer was described by Huggins et al. in 1941, who noted that prostate cancer activity was increased with androgen injections while castration and estrogen injections were beneficial to men with metastatic disease. Huggins' discoveries regarding hormone therapy in prostate cancer led to a Nobel Prize in medicine in 1966.

ADT can be achieved surgically (orchiectomy) or pharmacologically. Pharmacologic agents with androgen suppressing properties include luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, estrogens, anti-androgens (steroidal and non-steroidal), and adrenal androgen inhibitors. These agents can be administered according to several regimens for patients with advanced disease including monotherapy, combined androgen blockade (CAB; orchiectomy or LHRH agonist plus a non-steroidal anti-androgen), and intermittent androgen deprivation. In an intermittent ADT regimen, ADT therapy is usually stopped when prostate-specific antigen (PSA) levels drop below a pre-specified level and is reinitiated when the levels rise again.

ADT, though effective, is associated with numerous adverse events. In addition, patients eventually develop hormone-refractory disease and no longer respond to ADT. A recently published review of major adverse effects reported that prostate cancer patients treated
with ADT had an increased risk of overall fracture (summary risk of 1.23, 95% CI 1.10 – 1.38) compared to men who had prostate cancer but did not receive ADT.\(^3\) Furthermore, patients treated with ADT were at a 17% increased risk of cardiovascular mortality [summary hazard ratio (HR) of 1.17; 95% CI 1.07 – 1.29]. An elevated risk of diabetes was also identified. In addition to cardiovascular outcomes, diabetes and fracture risk, other adverse events associated with ADT therapy that affect quality of life include hot flashes and sexual dysfunction (SDF).

It has been suggested that the frequency of adverse effects associated with androgen deprivation may be managed through use of an intermittent treatment schedule.\(^8\) It has also been suggested that the time to hormone independence may be increased by implementing ADT on an intermittent basis based on pre-clinical data.\(^9,10\) The potential benefits of intermittent ADT relative to continuous ADT have not been fully characterized, though there is evidence to suggest that overall survival (OS) outcomes are similar for both strategies. The majority of studies that have compared intermittent to continuous ADT report no difference in overall and/or progression-free survival (PFS).\(^11,12,13,14\) The majority of these studies have only been published in abstract form. The potential savings associated with administering ADT on an intermittent schedule must also be weighed from a policy perspective as decisions about resource allocation become increasingly important for health care decision makers.

Cost-effectiveness analysis allows the evaluation of both costs and outcomes of healthcare interventions by using a ratio of net healthcare costs to net health benefits.\(^15\) The main objective of such analyses is to "identify, measure, value and compare the costs and consequences of alternatives being considered".\(^16\) This type of analysis can be useful when trying to make decisions about resource allocation with the goal of optimizing health benefits under resource constraint.\(^17,18\)

In order to maximize the usefulness of a cost-effectiveness analysis for decision makers and allow comparison across interventions, a universal measure of health, such as life
expectancy (e.g. life years gained) or quality-adjusted life expectancy (e.g. quality-adjusted life year or QALY, or quality-adjusted life months or QALM) is required. The benefit of using QALYs or QALMs is that both life expectancy and quality of life are considered by multiplying the duration of life by a standard weight, such as a utility.

Utilities are a measure of preference under uncertainty which can be used to reflect the value of various different health states to individuals. By multiplying the duration of life in various health states by the corresponding utility and summing these values over the entire life expectancy of an individual, an estimate of the total QALYs is obtained. Therefore, interventions which reduce the amount of time spent in health states that are less preferred may result in greater QALYs compared to an alternative intervention even though overall life expectancy is shorter.

1.2 Purpose of the Study

From a clinical perspective, there is interest in intermittent ADT as an alternative to continuous ADT for patients with prostate cancer because of the potential benefits in terms of quality of life and overall tolerability. Nevertheless, the potential benefits must be considered in the context of the relative effects of intermittent ADT on the OS of these patients. Currently, there is some evidence to suggest that intermittent ADT results in similar OS outcomes compared to continuous ADT. Based on what is available in the literature and what has been presented at key conferences, OS does not appear to be lower for patients on intermittent ADT though they may be more likely to die of prostate cancer and less likely to die from other causes than patients treated on a continuous basis. These differences suggest that there may be tradeoffs to consider when determining which strategy to use in patients.

Data about the relative differences in AEs and quality of life between intermittent ADT and continuous ADT are less robust, though these effects may directly impact the quality of life of patients or result in additional costs to the health care system. For example, impaired sexual function is a side-effect of reduced levels of testosterone which has a negative effect
on the quality of life of men receiving ADT. Similarly, men experiencing hip fractures or developing cardiovascular disease require additional medical intervention and may require ongoing care as a result. Intermittent ADT is thought to result in fewer of these types of AEs by allowing testosterone recovery.\(^8\)

From a policy perspective, in addition to reducing the costs associated with treating some of the AEs of ADT, intermittent ADT may lead to additional cost savings as a result of reducing the use of expensive hormone therapies. A cost-effectiveness framework would allow all of the relevant data to be considered in order to evaluate the overall predicted effect of intermittent ADT on health as well as cumulative costs. Areas where there is significant clinical uncertainty could also be identified. This type of analysis would also provide additional information about the possible clinical tradeoff for selected subgroups such as those who have preexisting conditions.

Given the potential benefits, the objective of the present analysis was to evaluate the incremental cost per QALM of intermittent ADT compared to continuous ADT based on the available evidence. Secondary objectives were to compare cumulative incidence of key adverse events associated with ADT including: hip fractures, incident cardiovascular disease (CVD), and sexual dysfunction (SDF).
2 Review of the Literature

2.1 Efficacy of ADT

2.1.1 Monotherapy

The beneficial effects of orchiectomy in men with stage III and IV prostate cancer were demonstrated in randomized trials conducted by the Veterans Administration Co-operative Urological Research group in the late 1960’s.\textsuperscript{20,21} Although a PFS benefit was observed, OS was not significantly different. A meta-analysis of ADT monotherapies for patients with advanced prostate cancer found no statistically significant differences in survival rates for diethylstilbestrol (DES) versus orchiectomy or LHRH agonists versus orchiectomy or DES.\textsuperscript{22} Results of the analysis also found no significant difference among the various LHRH agonists. The authors also reported that survival rates with non-steroidal anti-androgens appeared to be lower compared to orchiectomy, DES, or LHRH agonists.

2.1.2 Combined ADT

Studies comparing CAB to ADT monotherapy in patients with advanced prostate cancer have also been conducted with conflicting results. Dijkman et al. reported results from a randomized trial comparing orchiectomy to nilutamide plus orchiectomy in patients with stage D2 disease and reported median OS of 27.3 months for combined therapy versus 23.5 months for orchiectomy (p=0.033).\textsuperscript{23} A study by Denis et al. comparing goserelin acetate and flutamide to bilateral orchiectomy in metastatic prostate cancer (M1a or M1b) reported an OS of 34.4 months for combined ADT compared to 27.1 months for orchiectomy (p=0.02).\textsuperscript{24} In the studies by Denis et al. and Dijkman et al. median time to objective progression for men receiving CAB was reported as 133 weeks (30.7 months) and 21.2 months, respectively. Dijkman et al. also reported that at year five, 20% of patients receiving combined ADT had not yet progressed. Objective progression in the Dijkman trial was based on criteria developed by the National Prostatic Cancer Project.\textsuperscript{25} Denis et al.
defined objective progression using parameters including: primary tumor size, regional lymph nodes, distant lymph nodes, bone, lung, and liver metastases.

A statistically significant difference in OS has also been reported in meta-analyses. Caubet et al. reported a relative risk of a non-steroidal anti-androgen (NSAA) plus an LHRH agonist or orchiectomy versus LHRH or orchiectomy alone of 0.78 (95% CI 0.67 - 0.90) and 0.84 (95% CI 0.76 – 0.93) for OS in patients with advanced prostate cancer using two different methods. Schmitt et al. reported pooled odds ratios (OR) for OS of 1.03 (95% CI 0.85 - 1.25), 1.16 (95% CI 1.00 to 1.33), and 1.29 (95% CI 1.11 to 1.50) for CAB compared to castration alone at one, two, and five years, respectively. Schmitt et al. reported pooled odds ratios (OR) for OS of 1.03 (95% CI 0.85 - 1.25), 1.16 (95% CI 1.00 to 1.33), and 1.29 (95% CI 1.11 to 1.50) for CAB compared to castration alone at one, two, and five years, respectively.27 PFS was improved at 1 year (OR = 1.38; 95% CI 1.15 to 1.67). There were no differences detected in PFS at later follow-up. The pooled OR at two years and five years was 1.19 (95% CI 0.97 to 1.46) and 1.14 (95% CI 0.77 to 1.68), respectively. A meta-analysis of 21 trials conducted by Samson et al. also found no statistically significant difference in OS rates at 2 years for CAB compared to monotherapy with LHRH agonists or orchiectomy.28 The difference in survival at five years statistically favored CAB (HR = 0.871; 95% CI 0.805– 0.942) though the pool of included trials was smaller (n=10).

Another meta-analysis reported no significant difference in survival rates for CAB vs monotherapy at five years.29,30 In a 2000 update to their 1995 analysis, the Prostate Cancer Trialists’ Collaborative Group reported 5-year survival rates of 25.4% versus 23.6% (2p = 0.11) for CAB therapy compared to monotherapy.29 Results for cyproterone acetate were unfavourable (5-year OS 15.4% CAB versus 18.1% monotherapy, 2p = 0.04 adverse) while those for nilutamide and flutamide were slightly favourable (5- year OS 27.6% CAB versus 24.7% monotherapy, 2p = 0.005).

2.2 Adverse Effects of ADT

2.2.1 Cardiovascular disease

Evidence regarding the effects of ADT on cardiovascular outcomes has been mixed.31 Two observational studies have reported that men receiving gonadotropin-releasing hormone
(GnRH) agonists for locoregional prostate cancer had a higher rate of incident coronary heart disease (CHD), myocardial infarction (MI), and sudden cardiac death than those who did not receive ADT.\textsuperscript{32,33} In a retrospective study of 73,196 men aged 66 or older (mean 74.2 ± 5.8 years) with locoregional prostate cancer, Keating et al. used Medicare data from the Surveillance, Epidemiology and End Results database to evaluate the effects of GnRH agonists on cardiovascular outcomes.\textsuperscript{32} The authors reported incidence rates of CHD for men receiving GnRH of 72.3 per 1,000 patient years (95% CI 64.2 to 69.4) compared to 61.3 per 1,000 patient years (95% CI 60.2 to 60.4) in men not receiving ADT. A statistically significant difference was reported for the risk of incident diabetes (HR 1.44; 95% CI 1.34 to 1.55), incident CHD (HR 1.16; 95% CI 1.10 to 1.21), MI (HR 1.11; 95% CI 1.01 to 1.21), and sudden cardiac death (HR 1.16; 95% CI 1.05 to 1.27) for GnRH compared to no ADT; for men who had orchiectomy, only the risk of incident diabetes was significant.

These results were confirmed by Keating et al. in a similar, smaller study of 37,443 men (mean age 66.9 ± 8.6 years) in the Veterans Healthcare Administration though rates of incident diabetes, incident CHD, and sudden cardiac death in men receiving GnRH were higher than the earlier study.\textsuperscript{33} For example, the reported unadjusted rate of incident CHD in men treated with GnRH was 144.0 per 1,000 person years (95% CI 137.5 to 152.2)\textsuperscript{33} compared to only 72.3 per 1,000 patient years in the earlier study.\textsuperscript{32} The study of data from the Veterans Healthcare Administration also provided data for men receiving combined androgen blockade and oral anti-androgen therapy in addition to those receiving only GnRH.\textsuperscript{33} Interestingly, in patients receiving CAB (1,838 individuals) only incidence rates of diagnosed CHD were significantly higher (HR 1.27; 95% CI 1.05 to 1.53) compared to those receiving no ADT. In addition, no increased risk was found for men treated with an oral anti-androgen.

A third US study reported a 20% increase in the risk of cardiovascular morbidity in men receiving ADT. In this study a broad definition, which included time to first cardiovascular event or death, was used and no information on specific cardiovascular outcomes was provided.\textsuperscript{34} Tsai et al. reported that ADT use was associated with higher rates of
cardiovascular mortality in men with local prostate cancer treated with radical prostatectomy (mean duration of ADT use 4.1 months).\textsuperscript{35}

In contrast to these findings from US sources, a study of administrative databases from Ontario, Canada by Alibhai et al. reported an increased risk of incident diabetes (HR 1.16; 95% CI, 1.11 to 1.21) for men treated with ADT but not acute MI (HR, 0.91; 95% CI, 0.84 to 1.00) or sudden cardiac death (HR, 0.96; 95% CI, 0.83 to 1.10).\textsuperscript{36} In addition, post hoc analyses from several RCTs have reported no relationship between ADT and cardiovascular risk.\textsuperscript{31} Roach et al. reported no significant difference in fatal cardiac events at ten years for men with locally advanced prostate cancer receiving neo-adjuvant ADT with external beam radiotherapy versus those who received no ADT.\textsuperscript{37}

Despite the conflicting evidence, periodic follow-up of patients in whom ADT is initiated has been advised in a joint statement from the American Heart Association, American Cancer Society and American Urological Association.\textsuperscript{31}

\subsection*{2.2.2 Fracture risk}

In a Canadian study by Lau et al. no significant association was found between prostate cancer and fracture risk while there was a significant association between ADT and fracture.\textsuperscript{38} The adjusted OR for current and past ADT were 1.71 (95% CI: 1.13 - 2.58) and 2.42 (95% CI: 1.42-4.12), respectively. Decreases in bone mineral density (BMD) resulting from ADT have been reported in multiple studies.\textsuperscript{39,40,41,42,43} Greenspan et al. reported that men with prostate cancer who initiated ADT had a five- to ten-fold increased loss of bone density compared with healthy controls as well as men with prostate cancer who did not receive ADT.\textsuperscript{43} Kiratli et al. reported a significant trend for decreased hip BMD with increasing years of ADT compared to age-matched controls. Fractures resulting from low BMD, especially hip fractures, are associated with significant morbidity, mortality, and negative effects on quality of life.\textsuperscript{45,46,47}

While Alibhai et al. found no difference in cardiovascular outcomes, they reported that men treated with ADT were at a higher risk of fragility fractures compared to those who did not
receive ADT (HR, 1.65; 95% CI, 1.53 to 1.77). Similar results were reported in a recent population-based study of 742 men (mean age at diagnosis 68.2 ± 8.9 years) with prostate cancer, 16% of whom had advanced disease, from Olmsted County, Minnesota in the US. Compared to men with untreated cancer, the risk of fracture in men who received ADT therapy was 1.7-fold higher. While no association was found between prostate cancer itself and fracture risk in a Canadian population-based study, both current (OR 1.71; 95% CI 1.13 - 2.58) and past (OR 2.42; 95% CI 1.42-4.12) ADT use were associated with an increased risk of fracture.

An increased risk of hip fracture among patients treated with GnRH agonists has been reported in several studies. Smith et al. reported a relative risk of 1.76 (95% CI 1.33 to 2.33) for hip fracture in men who received a GnRH agonist compared to those who did not receive GnRH agonists. The incidence of hip fracture was 1.16% per 100 person-years versus 0.66% per 100 person-years (p<0.001). Similarly, Shahinian et al. reported that 4.06% of men receiving ADT experienced a hip fracture twelve to 60 months after diagnosis of prostate cancer compared to only 2.06% of men who received no ADT (p<0.001). Overall fracture rates in men who survived at least five years after diagnosis were 12.6% for men not receiving ADT compared to 19.4% for men who did receive ADT (p<0.001). In a study of administrative databases from Ontario, Canada, Alibhai et al. reported an increased risk of fragility fracture (HR 1.65, 95% CI 1.53–1.78) in prostate cancer patients aged 66 or older receiving continuous ADT for at least 6 months compared to patients who had never been treated with ADT. The HR for any fracture was HR 1.46 (95% CI 1.39–1.54).

2.2.3 Sexual Dysfunction

Potosky et al. found that 80% of men with newly diagnosed localized prostate cancer who were sexually potent prior to diagnosis and treated with ADT reported being impotent after 1 year compared to 30% of those who were not receiving ADT. Fowler et al. evaluated the effects of ADT on quality of life in men who had undergone prostatectomy for prostate cancer and reported a significant difference in the number of patients who reported having sexual intercourse in the previous month (2% of those treated with ADT versus 12% of those
not treated with ADT, p<0.0001). Furthermore, 69% of men receiving ADT reported no days of feeling sexual drive compared to only 29% of non-androgen-deprived men (p<0.0001).

In a retrospective study of self-reported sexual function in men (mean age 71.7 years) with prostate cancer following initiation of ADT, DiBlasio et al. found that 57 of 395 men had erectile dysfunction (ED) following ADT therapy. New-onset ED was observed in 70% of cases reported. The majority of men who reported ED following ADT had received ADT on a continuous basis (51 of 57 men); however, only 36 of 395 men in the study had received intermittent ADT.

2.3 Intermittent versus Continuous ADT

To identify studies comparing intermittent and continuous ADT, a literature search was conducted using Medline, EMBASE and the Cochrane Library from 1995 to 2011 using keywords “prostate cancer AND (intermittent androgen deprivation OR intermittent androgen suppression)”. The search was limited to studies published in English. In addition, references identified in key review papers were hand searched to identify any additional studies. Studies of interest were randomised controlled trials comparing intermittent to continuous ADT in men with advanced prostate cancer.

There were few fully published randomised controlled trials directly comparing continuous ADT to intermittent ADT identified in the literature search. Findings from studies presented at conferences and published in abstract form (identified by hand-searching the references of review papers) have suggested that survival outcomes are similar but despite these data, treatment guidelines published by the American Society of Clinical Oncology from 2004 and 2007 reported a lack of evidence to support use of an intermittent treatment schedule over continuous androgen blockade. A systematic literature review published in 2007 identified only 5 trials comparing intermittent treatment to continuous ADT. The trials were reported to have relatively small sample sizes as well as limited survival data. A more recent review by Abrahamsson published in 2010 found 19 phase II trials and published
results from 8 phase III trials, though the majority of these were published in abstract form only.\(^8\)

A further challenge is that no standard treatment regimen has been used in trials of intermittent ADT. In clinical studies of continuous versus intermittent ADT, different types of ADT have been used. These include: cyproterone acetate,\(^{11,59}\) goserelin + bicalutamide,\(^{13}\) buserelin + nilutamide,\(^{12,60}\) leuprolide + flutamide,\(^{14}\) and goserelin + flutamide\(^{61}\).

In addition to variations in the type of ADT administered, differences in cycle lengths have been reported. In trials comparing intermittent ADT to continuous ADT, there is usually an induction period followed by randomization for those patients whose PSA levels drop to $< 4$ ng/mL. Treatment with ADT in the intermittent arm is reinitiated when the PSA levels rise and reach a predetermined level (e.g. PSA $> 10$ ng/mL or PSA $> 20$ ng/mL). In a meta-analysis of phase II trials, Shaw et al. reported a mean number of two cycles per patient with a median time off therapy of 15.4 months (median follow-up 39 months).\(^{62}\) The literature review by Abrahamsson reported that there were differences both in the number of cycles and the duration of the on and off treatment phase.\(^8\) In general, there was greater variability in the duration of the off-treatment phase compared to the duration of the on-treatment phase. In a study reporting on cycling characteristics of intermittent ADT in 61 men (mean age 70 years) without clinically apparent metastatic prostate cancer (29 of 61 patients were stage T3 disease at diagnosis), Grossfeld et al. reported that the time off therapy decreased with subsequent cycles both in absolute months off therapy and as a percentage of the total time per cycle.\(^{63}\) In this study, the mean follow up from the start of therapy was 30 months (range 7 to 60 months) and ADT was stopped if PSA reached a nadir of $< 0.1$ ng/mL if patients had prior local therapy or $< 4.0$ ng/mL for those with no prior local therapy. ADT was reinitiated if serum PSA was $\geq 50\%$ of pre-treatment levels, PSA $> 10$ ng/mL, or if the patient requested re-initiation.
2.3.1 Overall Survival

Despite the differences in the use of intermittent ADT, most trials comparing intermittent ADT to continuous ADT have reported no differences in OS. Calais da Silva et al. reported a HR for OS of 0.99 (95% CI 0.80 - 1.23) for continuous therapy with cyproterone acetate and an LHRH agonist (169 deaths) compared to intermittent therapy (170 deaths). Of note, deaths from cancer (HR 0.80; 95% CI 0.60 to 1.06) were less common in the continuous arm while death due to CVD (HR 1.32 adjusted for excess CVD at baseline; 95% CI 0.87 to 1.99) and other causes (HR 1.38; 95% CI 0.81 to 2.36) were more common. None of these differences reached significance. These results confirmed those from an earlier analysis of the same study, in which the authors reported 162 deaths in the intermittent arm versus 159 deaths in the continuous arm (HR 1.03 intermittent versus continuous ADT; 95% CI 0.83 – 1.28).  

Miller et al. reported a median OS of 53.8 months for continuous therapy compared to 51.4 months for intermittent ADT (p =0.658) in patients with advanced prostate cancer (stage T1-4N1-3M0 or T1-4N0-1M1; D1 or D2). The HR was not reported and the proportion of patients with metastatic disease was not provided. Mottet et al. reported median OS of 1560 days for continuous ADT (leuprolide and flutamide) compared to 1265 days for intermittent ADT (p = 0.74) in men with metastatic prostate cancer suggesting no difference between the two regimens. Langenhuijs et al. also reported no difference in OS for continuous versus intermittent therapy in patients with advanced prostate cancer treated with buserelin and nilutamide. No HR or median survival times were reported. 

Intermittent ADT has also been compared to continuous ADT in men experiencing PSA relapse. Crook et al. reported that intermittent ADT was non-inferior to continuous ADT in a study of 1,386 men with prostate cancer. Median OS was 8.8 vs 9.1 years on intermittent ADT and combined ADT, respectively (HR 1.02, 95%CI 0.86-1.21). More disease-related (122 vs 97) and fewer unrelated (134 vs 146) deaths were reported for those in the intermittent arm compared to those receiving continuous ADT.
2.3.2 Progression-Free Survival

While the evidence regarding OS is more consistent with regards to the relative efficacy of intermittent ADT versus continuous ADT, some studies have suggested differences in PFS.\textsuperscript{8,61,64,65} It should be noted that there are differences in the way progression is defined in clinical trials of advanced prostate cancer patients, as shown in Table 1. For example, Calais da Silva et al. defined progression as objective (distant metastasis or new metastatic sites) or subjective (biochemical progression that was an increase of the PSA level by 20% on two successive occasions at least 1 month apart while on treatment, increase in pain by two increments or the worsening of performance status by two decrements).\textsuperscript{11} The proportion of patients who were progression free at 80 months was estimated to be 55% from the published Kaplan-Meier curve. The majority of the patients in this trial were M0 at the start of the trial. Miller et al. defined progression as clinical and/or biochemical progression due to any reason.\textsuperscript{13} The reported median PFS in men with clinical stage T1-4N1-3M0 or T1-4N0-3M1 disease was 16.6 months compared to 11.5 months for intermittent and continuous ADT, respectively (p = 0.1758). Patient demographic data was not available to determine what proportion of patients had metastatic disease. Mottet et al. defined progression in metastatic prostate cancer patients as a PSA level > 4 ng/mL and increasing (three consecutive monthly assays) and/or clinical progression.\textsuperscript{14} Median PFS was reported to be 452 days for continuous ADT compared to 620 days for intermittent ADT (p = 0.73). Langenhuijsen et al. reported median time to clinical progression or PSA escape in men with advanced cancer of 18.0 months and 24.1 months for intermittent and continuous ADT, respectively.\textsuperscript{12} The proportion of patients by metastatic status at baseline was not available.

In contrast to these findings, in a smaller study of 68 patients with advanced hormone-naïve prostate cancer, de Laval et al. reported 3-year risk of progression to androgen independent biochemical progression of 38.9% ± 11.2% for continuous ADT compared to 7.0% ± 4.8% for intermittent ADT.\textsuperscript{61} In this study, the mean follow-up time was short (30.8 months). In addition, in the study by Crook et al. which included patients with PSA relapse, a significant difference in time to hormone-refractory disease was reported for intermittent ADT.
compared to continuous ADT (HR 0.80; 95%CI 0.67-0.98) though this was published in abstract form only.\textsuperscript{65}

As this thesis was being written, an additional analysis of data from the study by Langenhuijsen et al. looked at the predictive value of PSA for progression in men with metastatic prostate cancer.\textsuperscript{12,66} The analysis focused on 173 men with metastatic prostate cancer who experienced progression. The authors reported that the 2-year risk of progression was significantly higher for patients with a PSA nadir of \( \leq 0.2 \) ng/ml that were treated with intermittent ADT compared to continuous ADT 53\% vs 31\%; (p=0.03). Progression was defined based on the European Organisation for Research and Treatment of Cancer (EORTC) criteria for clinical progression in 1989 as follows: any lesion increases in size or any new lesion appears, regardless of what the response of the other lesions has been; increase in any measurable deposit by \( > 25\% \); increase in volume of primary tumor by \( > 50\% \); significant deterioration in symptoms, decrease in weight, or decrease in performance status; increase in acid or alkaline phosphatase alone is not be considered an indication of progression. These findings suggest that there may be some patients in whom intermittent ADT may not be as effective as continuous ADT though these were data based on a limited population in a post-study analysis.
<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Population</th>
<th>Definition of Progression</th>
<th>Progression-Free Survival Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Silva(^{11}) (2009)</td>
<td>Histologically confirmed prostate adenocarcinoma, cT3–cT4 M0, cT3–cT4M1, PSA ≥ 4 ng/ml, age &lt; 80 years, and World Health Organisation performance status 0–2</td>
<td><strong>Objective</strong>: distant metastases or new metastatic sites <strong>Subjective</strong>: presence of at least two of the following 3 criteria: (1) biochemical progression that was an increase of PSA level by 20% on 2 successive occasions, ≥ 1 mos apart, while on treatment; (2) an increase in pain by 2 increments; or (3) the worsening of the performance status by 2 decrements</td>
<td>HR for time to any progression = 0.81 (95%CI 0.63–1.05, p = 0.11) for CON versus INT ADT</td>
</tr>
<tr>
<td>Miller(^{13}) (2007)</td>
<td>Histologically confirmed prostate adenocarcinoma stage T1–4N1–3M0 or T1–4N0–3M1 (D1 or D2)</td>
<td>Clinical and/or biochemical progression of the disease despite androgen suppression; no further information provided (abstract only)</td>
<td>Median time to disease progression: INT ADT = 16.6 months; CON ADT = 11.5 months (log rank test, p=0.1758)</td>
</tr>
<tr>
<td>Mottet(^{14}) (2009)</td>
<td>Patients with newly diagnosed metastatic prostate cancer</td>
<td>PSA &gt; 4 ng/ml and increasing (3 consecutive monthly assays) or clinical progression; no further information provided (abstract only)</td>
<td>Median progression free survival: INT ADT = 620 days; CON ADT = 452 days (p=0.736)</td>
</tr>
<tr>
<td>Langenhuijsen(^{14}) (2008)</td>
<td>Patients with advanced prostate cancer. See reference (^{66}) below for further details</td>
<td>Clinical progression; see reference (^{66}) below for further details PSA escape defined as PSA &gt; 50 ng/mL</td>
<td>Median time to PSA escape or clinical progression: INT ADT = 18.0 mos; CON ADT = 24.1 mos</td>
</tr>
<tr>
<td>Langenhuijsen(^{66}) (2011)</td>
<td>Histologically confirmed prostate cancer with positive lymph nodes or distant metastases (T2-4N1-3M0 or T2-4NxM1)</td>
<td>EORTC definition of clinical progression (1989): any lesion increases in size or any new lesion appears, regardless of what the response of the other lesions has been; increase in any measurable deposit by &gt; 25%; increase in volume of primary tumor by &gt; 50%; significant deterioration in symptoms, decrease in weight, or decrease in performance status; increase in acid or alkaline phosphatase alone is not be considered an indication of progression</td>
<td>2-year risk of progression: No significant difference for INT versus CON ADT on all predictive factors tested except for patients with PSA nadir ≤ 0.2ng/mL INTADT = 53 ± 7.6%; CON ADT = 31 ± 8.3% (p = 0.03)</td>
</tr>
<tr>
<td>de Leva(^{61}) (2003)</td>
<td>Histologically confirmed prostate adenocarcinoma &lt; 80 years and having (1) locally advanced (stage T3 or T4), and/or (2) metastatic (N+ and/or M+) tumors, or (3) relapsing prostate cancer following prostatectomy for clinically localized prostate cancer (classified as stage T1/T2 N0 M0).</td>
<td>Increasing total serum PSA level of ≥ 10 ng/mL despite continued complete ADT; ≥ 3 successive determinations of increasing total serum PSA concomitant with castrate-like serum testosterone levels; date of progression was when the first serum PSA measurement was ≥ 10 ng/mL.</td>
<td>Estimated 3-year progression rate: INT ADT = 7.0 ± 4.8%; CON ADT = 38.9 ± 11.2% (p = 0.0052)</td>
</tr>
<tr>
<td>Klotz(^{64}) (2011)</td>
<td>Men with rising PSA &gt; 3.0 ng/ml &gt; 1 year post radical radiotherapy, either initial or salvage, for localized prostate cancer.</td>
<td>Time to hormone refractory state; no further information provided (abstract only)</td>
<td>HR for time to hormone refractory state: INT ADT versus CON ADT = 0.80 (5%CI 0.67-0.98; p = 0.024)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; PSA = prostate specific antigen; ADT = androgen deprivation therapy; INT = intermittent; CON = continuous, mos = months.
2.3.3 Adverse Effects and Quality of Life

There are limited data directly reporting differences between intermittent ADT versus continuous ADT on key adverse events or quality of life. Calais da Silva et al. reported that a greater proportion of patients treated with continuous ADT experienced hot flushes (30.0% vs 19.7%, p<0.01), gynaecomastia (19.5% vs 12.4%, p = 0.02), headache (12.3% vs 7.4%, p = 0.06), and skin complaints (6.8% vs 2.7%, p = 0.03) compared to those on intermittent therapy based on data from 766 patients and a median follow-up time of 51 months. In addition, patients on intermittent therapy experienced fewer sexual problems and reported greater sexual activity compared to those who received continuous ADT. A total of 28% of men on intermittent therapy reported being sexually active 15 months after randomization compared to only 10% of those in the continuous arm (no p value was provided). Interestingly, shortly after randomization, when those in the intermittent arm were off therapy, sexual activity levels returned to pre-treatment levels. Despite these findings, with a few exceptions, there was no significant difference between the two treatment arms in most domains of quality of life measured.

Data from a larger cohort of the Calais da Silva et al. study reported that three times as many patients in the continuous arm experienced side effects at least once compared to the intermittent arm. In addition, while no difference in sexual activity was reported at randomisation, sexual activity increased to 33% (6 months), 29% (12 months), and 28% (24 months) in the intermittent group. In contrast, in the continuous arm the corresponding percentages were 20% (p=0.002), 19% (p=0.06), and 8% (p=0.0001), respectively. The authors concluded that quality of life (namely sexual function) was better in the intermittent arm, but no quality of life scores were reported.

The effects of intermittent versus continuous ADT on CVD were not directly measured by Calais da Silva et al. but there were more deaths due to CVD in the continuous arm than in the intermittent arm (52 versus 41). The difference was not statistically significant. No data on fracture risk were reported.
Miller et al. also reported that self-assessed sexual function was better for men receiving ADT on an intermittent basis compared to continuous ADT.\textsuperscript{13} Crook et al. reported that men with PSA relapse following radiotherapy reported quality of life benefits for intermittent ADT on measures of desire for sexual activity (\(p < 0.01\)) and erectile function (\(p < 0.01\)).\textsuperscript{65} Other differences favouring intermittent ADT included physical function (\(p < 0.01\)), fatigue (\(p < 0.01\)), urinary problems (\(p = 0.01\)), and hot flushes (\(p < 0.01\)). No differences in other adverse effects, including myocardial events or fractures, were reported. Additional details are lacking as this study has only been published in abstract form.

Spry et al. compared quality of life scores during both the on and off treatment phases of ADT therapy.\textsuperscript{68} The authors reported that during the on-treatment phase, men treated with maximum androgen blockade (MAB) had statistically significant deterioration on 12 quality of life scales (\(p < 0.01\)). After 9 months of ADT, complete loss of interest in sex increased from 37.2\% prior to treatment to 72.2\%, and complete sexual inactivity rose from 54.3\% to 86.9\%. During the off-treatment phase, significant improvements were observed for emotional function, sexual function, fatigue, sleep and hot flushes. Interestingly, disease extent at baseline was not a factor for recovery.

Spry et al. also evaluated the effects of intermittent ADT on BMD in men with prostate cancer and no metastatic bone disease.\textsuperscript{69} The authors reported that loss of BMD at the hip and spine was attenuated for men treated with intermittent ADT compared to those treated with continuous ADT. During the off-treatment phase, hip BMD declined at a rate of 0.6\% and 0.8\% one and two years after a nine month initial period of ADT therapy. These results were consistent with those reported by Higano et al. who reported that BMD at the hip declined by a smaller percentage after androgen suppression therapy was stopped in 16 men with prostate cancer and no metastatic bone disease.\textsuperscript{70} Hip BMD declined by -0.01\% from the time androgen suppression therapy was stopped to the end of the off-treatment phase or after 1 year, depending which came first. In contrast, hip BMD declined by 2.5\% during the nine month period of androgen suppression therapy. Yu et al. also reported that hip BMD decreased by a smaller percentage during the off-treatment phase of ADT
compared to the on-treatment phase in men with biochemical recurrence during the first cycle of intermittent ADT.\textsuperscript{71} Attenuation of "on-treatment" BMD loss during the "off-treatment" phase was also noted for subsequent cycles of ADT. Despite the evidence suggesting that intermittent ADT may reduce fracture risk compared to continuous ADT based on a slower rate of BMD loss, data comparing fracture rates in men with advanced disease are limited. As noted previously, Crook et al. reported no significant difference in fracture rates for men with PSA relapse following radiotherapy; rates were not reported by fracture type.\textsuperscript{65}

2.4 Cost-Effectiveness of ADT

Bayoumi et al. evaluated the cost-effectiveness of anti-androgen therapy for advanced prostate cancer based on a cohort of men aged 65 years with local recurrence of prostate cancer over a 20-year time horizon from a societal perspective.\textsuperscript{72} The authors reported that orchiectomy was likely to be the most cost-effective treatment option. The result was sensitive to the quality of life associated with orchiectomy. CAB with orchiectomy and a non-steroidal anti-androgen was associated with 5.05 QALY, 6.49 LY, and costs of $20,700 US (all values discounted at 3% per year). In contrast, CAB with an LHRH agonist plus a non-steroidal anti-androgen resulted in costs of $40,300 US and similar survival outcomes (5.03 QALYs and 6.48 LY). Other studies have evaluated the cost effectiveness of CAB compared to monotherapy or orchiectomy alone.\textsuperscript{73,74} Hillner et al. reported an incremental cost per LY gained of $25,300 US for flutamide combined with an LHRH agonist or orchiectomy compared to LHRH monotherapy or surgery alone based on an analysis of men with M1 prostate cancer.\textsuperscript{74} Penson et al. reported an incremental cost per QALY for bicalutamide plus an LHRH agonist compared to monotherapy with an LHRH agonist of $20,053 at 10 years for men with stage D2 disease.\textsuperscript{73} The incremental cost per LY gained was $13,313. A Canadian study which used a population-based, retrospective analysis using data from the British Columbia Cancer Agency database reported an incremental cost of $1,768 per patient and an incremental cost per LY gained of $11,220 for CAB compared to ADT. It is
unclear what cost components were considered and survival was based on data from a meta-analysis.\textsuperscript{75}

Despite the potential benefits of intermittent ADT described in the literature from both a clinical and economic perspective, no studies were found that assessed the cost-effectiveness of intermittent ADT compared to continuous ADT. As described in Section 1.2, there is interest in the relative benefits of intermittent ADT compared to continuous ADT. The relationship between overall survival, quality of life, and costs for these two strategies can be evaluated in the context of a cost-effectiveness analysis to allow a comparison that considers all the relevant information that is available. Therefore, the objective of the present analysis was to evaluate the incremental cost per QALM for intermittent ADT compared to continuous ADT based on the available literature.
3 Methods

An economic evaluation was conducted to compare the incremental costs and health benefits of intermittent versus continuous ADT.

3.1 Economic Assumptions

Both a cost-effectiveness and cost-utility analysis were performed using a Markov individual-level microsimulation model using TreeAge® Pro Suite 2009. The model evaluates mean total costs and QALMs gained as well as total life months (LM) gained for each treatment strategy over a lifetime horizon using data collected from published sources. The incremental cost per QALM and LM was also calculated. A two-dimensional simulation (trials and sampling) was run for the base case with 5000 samples and 10,000 trials.

The perspective of the analysis is that of a third party payer. Therefore, only direct medical costs were considered. The model calculates costs and outcomes over a lifetime horizon. Patients are followed until death or they reach 100 years of age. In order to adjust the value of future benefits and costs to present values, all costs and outcomes were discounted at a rate of five percent annually in alignment with Canadian pharmacoeconomic analysis guidelines.19

3.2 Patient Population

Patients in the model are men with advanced prostate cancer, defined as stage T3/4 M0 or M1 disease, who are naïve to hormone therapy and starting ADT. The model assumes that approximately 31% of men have metastatic disease based on the population included in one of the key clinical trials comparing intermittent to continuous ADT.11 The mean age was 72.6 years at model entry and mean bone BMD was based on a normal distribution estimated from population means for men aged 70-79 (mean femoral neck BMD = 0.754 ± 0.131 g/cm²).76,77
It is generally understood that the prevalence of SDF increases with age.\textsuperscript{78} Due to differences in the way SDF is defined, it is difficult to quantify. In addition, data on SDF rates for patients managed with intermittent therapy are under-reported in the literature. To ensure that a consistent definition was represented in the model, the proportion of men with SDF was taken directly from the Calais da Silva study which reported on the effects of intermittent and continuous ADT on SDF before and after therapy.\textsuperscript{11} It was assumed that 65\% of patients had SDF at the start of the model based on the proportion of patients reporting sexual activity prior to the start of the trial as a measure of sexual functioning.

It was further assumed that 10.3\% of patients had prevalent CVD in each arm of the model.\textsuperscript{11} Since it was not known how many patients with or without CVD also had SDF, it was assumed that 10.3\% of each group (i.e. those with sexual function and those without sexual function at the start of the model) also had CVD. This approach assumes that the probabilities of these two comorbidities are independent of one another. Although there is evidence to suggest that men with ED are at a higher risk of experiencing CVD, the definition of SDF in the Calais Da Silva study was not limited to patients with ED.\textsuperscript{79} The link between SDF (as defined by Calais da Silva) and CVD is not known. No patients had prevalent hip fracture when entering the model.

### 3.3 Comparators

The model compares two interventions for patients with advanced prostate cancer: continuous administration of ADT versus intermittent administration of ADT. Continuous ADT is defined as ADT taken continually until progression to hormone refractory disease. Intermittent ADT, in contrast, is defined as cycles of both “on” and “off” treatment intervals. In clinical studies, the duration of “on” and “off” treatment cycles is determined by patients’ PSA levels relative to pre-specified thresholds. Data on PSA levels over time are often not reported in studies of intermittent ADT however, the mean and/or median time on and off treatment is sometimes reported. Therefore, intermittent ADT was modeled using a set time for the “on” and “off” treatment intervals in each cycle until progression to hormone refractory disease.
In the present analysis, for patients treated with intermittent ADT, it was assumed that the on-treatment phase was fixed at four months based on data suggesting that the on-treatment phase is less variable than the off-treatment phase. The time off therapy in the first cycle was based on the median time off therapy of 15.4 months reported by Shaw et al. in their meta-analysis of phase II studies of intermittent ADT. For each subsequent cycle, the time off therapy was assumed to decrease to 86% of the previous cycle.

Given the available evidence, it was assumed that the difference in health effects of continuous versus intermittent ADT are not dependent on the type of ADT selected but rather are due to the treatment schedule. Therefore, the model outcomes are based on the assumption that the same drugs are used in the same doses. Only the schedule in which the drugs are administered is assumed to differ. ADT was therefore defined as 9.5 mg of buserelin every 3 months plus 50 mg of bicalutamide daily based on the Cancer Care Ontario treatment regimen for prostate cancer.

3.4 Model Structure

Prostate cancer disease progression was represented in the model as three health states: stable disease (i.e. responding to hormones), hormone-refractory disease, and death. Due to the on-and off-treatment phases of intermittent therapy, stable disease was modeled as two health states; stable on-treatment and stable off-treatment with additional health states for those with comorbid conditions including: SDF, CVD, and/or hip fracture (year 1 and subsequent years). In total 35 health states were included with additional tracker variables to capture patient history in the model such as the occurrence of a hip fracture, incident CVD, incident SDF, time on treatment, and time with SDF. While other AEs were considered, from a modeling perspective, consideration was given to the overall complexity and computational requirements of including several different AEs. Therefore, the criteria used to determine which should be included in the analysis were: the event could significantly impact the quality of life of patients over a lifetime horizon and/or result in significant costs to the health care system for treatment, a difference in the occurrence of the event had been reported for men receiving ADT compared to those not on ADT, and
there was some evidence in the literature to suggest that intermittent ADT may be associated with fewer of these events. Based on the review of the literature presented in Section 2, the three AEs identified as most relevant were SDF, hip fractures, and incident CVD. Of note, incident diabetes was not included because it would require additional modeling to capture all of the downward effects and there were no data comparing intermittent to continuous ADT for this outcome/AE.

All patients start the model on treatment according to the following distribution across health states: 31% had stable disease, 58% had stable disease plus SDF, 4% had stable disease plus CVD, and 7% had stable disease and both SDF and CVD.

During each monthly cycle in the model, all individuals could progress to hormone-refractory disease, experience a hip fracture due to decreased BMD (maximum of two per individual), or die. Transitions from hormone refractory disease to stable disease were not permitted. Individuals without SDF or CVD could transition from any of the prostate cancer states (i.e. stable or hormone-refractory disease) to health states that included these comorbid conditions. Hip fracture and incident CVD were not permitted to occur in the same cycle. Note that hip fractures were modeled as separate states to reflect the first 12 months following the event (hip fracture year 1) versus subsequent years (hip fracture subsequent years). Patients could only remain in the hip fracture year 1 state for 12 cycles. In addition, patients could not experience a subsequent hip fracture in the first 12 months following an event, which is a limitation in the model.

For patients in the intermittent arm, transitions from the stable on treatment state to the appropriate stable off treatment state (based on prior history) occurred based on the cycling patterns estimated from available data as previously described. A schematic of the model is presented in Figure 1.
Figure 1. Diagram of Markov Monte Carlo Micro-Simulation Model

PCa = Prostate cancer, SDF = Sexual dysfunction, CVD = cardiovascular disease. Arrows represent transitions between states. Patients enter the model on treatment and have stable disease (31%), stable disease with SDF (58%), stable disease with CVD (4%), or stable disease with SDF and CVD (7%). During each cycle, patients could progress, experience a hip fracture, or die. In addition, individuals without SDF or CVD could develop de novo SDF and/or CVD during each cycle however, hip fractures could not occur in the same cycles as incident CVD. Patients experiencing a hip fracture were not permitted to experience a subsequent event while in a “hip fracture year 1” state. All patients in a “hip fracture year 1” state were forced to transition to “hip fracture subsequent years” states after 12 months. Transitions from the stable on treatment state to the stable off treatment phase (+ SDF, CVD, and/or hip fracture based on previous history or events) were only permitted in the intermittent arm based on a fixed on treatment phase of 4 months and a variable off treatment phase; in cycle 1 the off treatment phase was 15.4 months and the duration decreases by 86% in each subsequent cycle.

3.5 Model Inputs

All values used in the model were collected from available published sources or unpublished data where available. To allow probabilistic sensitivity analyses to be performed, distributions were used for key model inputs. The methods used to estimate these values are described in the following sections.

3.5.1 Progression-Free Survival

Transitions from stable disease to hormone refractory prostate cancer in the continuous ADT arm were modeled based on transition probabilities reported in the literature. Because different definitions of progression have been used, it was necessary to make some
assumptions when estimating transition probabilities. First, it was assumed that any progression for patients treated with hormone therapy reflected hormone refractory disease as it suggests patients are no longer responding to ADT treatment. In addition, objective progression rates were used based on the definitions used in each trial. Separate progression data for patients with stage T3/4 disease and metastatic disease were used in order to reflect differences in these populations.

To estimate the time to progression for a population of patients with advanced cancer (stage T3/T4, M0 or M1), a weighted average rate of progression was calculated based on the proportion of patients with metastatic versus stage T3/4 disease in the model population.

PFS rates for patients with stage T3/T4 disease were taken from Johansson et al. and weighted using methods previously described. The 10-year and 15-year PFS rates reported were 57.5% (95% CI 48.2% - 66.8%) and 46.6% (95% CI 32.7% - 60.5%) for patients with stage T3/T4 disease. Though similar data was also reported for patients with metastatic disease, use of data PFS from 10 to 15 years for patients with advanced disease was felt to lead to an underestimate of progression rates as these reflect the tail end of the PFS curve. Therefore, for patients with metastatic disease, median PFS data for patients with stage D2 disease treated with CAB from Dijkman et al. were used to calculate transition probabilities assuming a constant rate of progression. The reported median PFS was 21.2 months. To validate the model, the estimated PFS rate from the model predicted PFS curve was compared to the weighted average rate calculated directly from the two published studies in order to ensure consistency.

PFS in the intermittent ADT arm was calculated using the inverse of reported HRs for continuous versus intermittent ADT from Calias da Silva et al. Though de Laval et al. reported a significant difference in three year PFS rates for intermittent versus continuous ADT, the study was small with a short follow-up. The vast majority of trials identified did not report any differences in median PFS. Therefore, the data from the Calais da Silva
et al. trial was considered representative of the data in the literature. Transition probabilities for progression in the intermittent ADT arm of the model were calculated using the same methods as those used to estimate OS transition probabilities.

3.5.2 Non-Prostate Cancer-Specific Mortality

Estimates of non-prostate cancer mortality rates used in the model were based on age-specific data for males from Canadian life tables from Statistics Canada. Annual probabilities of mortality were converted to monthly rates assuming an exponential hazard function using the following equation:

\[ \text{Rate} = -\frac{\ln(1 - \text{probability})}{\text{time}} \] (Equation 1)

The monthly all-cause mortality rate was then multiplied by the RR of death for each health state as required. The methods used to derive non-prostate cancer specific mortality rates based on the presence or absence of CVD and/or hip fractures are described in the sections below. Monthly rates were then converted to probabilities using Equation 2 below:

\[ \text{Probability} = 1 - \exp(-\text{rate} \times \text{time}) \] (Equation 2)

Baseline characteristics, survival estimates, and adverse event input parameters used in the model are summarized in Table 2.

3.5.2.1 Cardiovascular Disease Mortality

Men with CVD are at an increased risk of death as a result of their disease. Evidence from clinical trials suggests that men treated with continuous ADT are at an increased risk of death due to CVD compared to intermittent ADT. The relative risk of developing incident CVD for intermittent ADT compared to continuous ADT has not been reported. Since the present analysis considers the RR of developing incident CVD for intermittent versus continuous ADT, the impact on survival was captured indirectly based on the increased risk of death associated with CVD rather than a direct estimate of the relative difference in death due to CVD. The RR of death for men with CVD in the model was estimated by
### Table 2. Baseline Characteristics, Adverse Event, and Survival Input Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(Expected) Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
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<tr>
<td>Mean age (years)</td>
<td>72.6</td>
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<td>11</td>
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<td>Baseline BMD – femoral neck (g/cm^2)</td>
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<td>Distribution between states at entry</td>
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<td>Stable disease on treatment</td>
<td>31.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease on treatment plus SDF</td>
<td>58.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease on treatment plus CVD</td>
<td>4.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease on treatment plus CVD and SDF</td>
<td>7.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Proportion of patients with metastatic disease</td>
<td>31.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Proportion of patients with non-metastatic disease</td>
<td>69.0%</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Discount Rate (Annual)</td>
<td>5.0%</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td><strong>Duration on/off treatment (INT arm only)</strong></td>
<td>4 months /variable</td>
<td>NA</td>
<td>Assumption, 11,63</td>
</tr>
<tr>
<td><strong>Survival (Monthly)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background mortality (Canadian life tables)</td>
<td>Varies by age</td>
<td>NA</td>
<td>81</td>
</tr>
<tr>
<td>Relative risk of mortality for patients with CVD</td>
<td>1.40 (0.70 - 2.10)</td>
<td>Log Normal</td>
<td>Assumption, 83</td>
</tr>
<tr>
<td>Relative risk of mortality – hip fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year after hip fracture</td>
<td>3.70 (3.31 – 4.14)</td>
<td>Log normal</td>
<td>84</td>
</tr>
<tr>
<td>Subsequent years</td>
<td>1.69 (0.96 – 2.87)</td>
<td>Log normal</td>
<td>84</td>
</tr>
<tr>
<td>Probability of death due to other causes - CONT *</td>
<td>0.70 (0.41 - 1.20)</td>
<td>Log Normal</td>
<td>Assumption, 11</td>
</tr>
<tr>
<td>HR for death due to other causes - INT vs CONT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCa specific survival rate (to calculate weighted rate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>0.018</td>
<td>NA</td>
<td>Assumption, 85</td>
</tr>
<tr>
<td>Stage T3/T4</td>
<td>0.003</td>
<td>NA</td>
<td>Assumption, 85</td>
</tr>
<tr>
<td>Probability of death due to PCa (weighted) CONT arm</td>
<td>0.008</td>
<td>Beta</td>
<td>Assumption, 11,85</td>
</tr>
<tr>
<td>Multiplier for PCa death from hormone refractory state</td>
<td>7.5</td>
<td>NA</td>
<td>Assumption, 76</td>
</tr>
<tr>
<td><strong>Progression (Monthly)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of progression (to calculate weighted rate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>0.033</td>
<td>NA</td>
<td>23</td>
</tr>
<tr>
<td>Stage T3/T4</td>
<td>0.004</td>
<td>NA</td>
<td>Assumption, 85</td>
</tr>
<tr>
<td>Probability of progression (weighted) CONT arm</td>
<td>0.013</td>
<td>Beta</td>
<td>Assumption, 11,85</td>
</tr>
<tr>
<td>HR progression INT arm</td>
<td>1.24 (0.95 - 1.59)</td>
<td>Log normal</td>
<td>Assumption, 11</td>
</tr>
<tr>
<td><strong>Adverse Effects of ADT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of de novo SDF INT arm (monthly)</td>
<td>0.005</td>
<td>Beta</td>
<td>Assumption, 8, 11,67</td>
</tr>
<tr>
<td>Probability of de novo SDF CONT arm (monthly)</td>
<td>0.022</td>
<td>Beta</td>
<td>Assumption, 11,85</td>
</tr>
<tr>
<td>Probability of incident CVD INT arm (monthly)</td>
<td>0.005</td>
<td>Beta</td>
<td>Assumption, 32</td>
</tr>
<tr>
<td>HR for incident CVD CONT arm</td>
<td>1.320</td>
<td>Log normal</td>
<td>Assumption, 11</td>
</tr>
<tr>
<td>Rate of BMD loss (g/cm^2) per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During ADT treatment</td>
<td>0.019 ± 0.005</td>
<td>Normal</td>
<td>Assumption, 69,76</td>
</tr>
<tr>
<td>Without ADT treatment</td>
<td>0.004 ± 0.001</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Reference BMD (g/cm^2) and SD for T-Score calculation</td>
<td>0.860± 0.120</td>
<td>NA</td>
<td>86</td>
</tr>
<tr>
<td>Probability of hip fracture (monthly)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk of subsequent hip fracture (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74 years of age</td>
<td>1.90 (1.37 – 2.65)</td>
<td>Log normal</td>
<td>76,</td>
</tr>
<tr>
<td>75-79 years of age</td>
<td>1.64 (1.24 – 2.17)</td>
<td>Log normal</td>
<td>76,82</td>
</tr>
<tr>
<td>80-84 years of age</td>
<td>1.41 (1.12 – 1.78)</td>
<td>Log normal</td>
<td>76,82</td>
</tr>
<tr>
<td>≥ 85 years of age</td>
<td>1.32 (1.04 – 1.68)</td>
<td>Log normal</td>
<td>76,82</td>
</tr>
</tbody>
</table>

* Other causes defined as the rate of death excluding CVD, hip fracture or prostate cancer. Numbers rounded. Weighted = weighted by proportion metastatic/non-metastatic BMD = bone mineral density; PCa = prostate cancer SDF = Sexual dysfunction; CVD = cardiovascular disease; INT = intermittent arm; CONT = continuous arm; SD = standard deviation; HR = hazard ratio.
comparing the cause-eliminated rate of death (major CVD) to the all-cause mortality rate from Statistics Canada data. This was calculated as the ratio of the age-adjusted all-cause mortality rate and cause-eliminated mortality rate (calculated as the difference between the age-adjusted all-cause mortality rate for Canadian males and the age adjusted mortality rate due to major CVD). For sensitivity analyses, the 95% CI for each estimated RR were assumed to be plus or minus 50%. Note that this ratio was only used to estimate the RR of death. The baseline all-cause mortality was taken from Canadian life tables.

3.5.2.2 Hip Fracture Mortality

Similarly, because men with hip fractures are at an increased risk of death and men receiving ADT are at risk of increased fractures, the non-prostate cancer specific rate of death was adjusted by applying a RR of death in cases where a fracture occurred. The excess risk of mortality in men with hip fractures relative to the general population extends for several years though it appears to be higher in the first year following the event than in subsequent years. The RR of death following a hip fracture applied in the model was based on data from a recent meta-analysis by Haentjens et al. which reported a pooled RR of death of 3.70 (95%CI 3.31 – 4.14) in the first year following the fracture. The RR of death in subsequent years used in the model was 1.69 (95% CI 0.96 – 2.87) based on an estimate of the average HR of all-cause mortality from year two to year 10 from the same study.

3.5.2.3 Mortality in Men with Hip Fracture and Cardiovascular Disease

In the case where both CVD and hip fractures are present, the estimated RR of death was calculated as the RR of death due to hip fracture multiplied by the RR of death due to CVD. This method was used due to a lack of data on the RR of death for men with both of these comorbid conditions relative to all-cause mortality. Furthermore, little information was available on hip fractures and CVD as competing risks of death. This approach may result in an overestimate of the overall RR of death in this population of men and is therefore a limitation in the analysis.
3.5.2.4 Death due to Other Causes

Death due to other causes, for the purposes of the model, is defined as death due to causes other than cancer, CVD or hip fracture.

3.5.2.4.1 Continuous ADT

The probability of death due to other causes for men on continuous ADT is based on all-cause mortality for men from Canadian life tables.\(^8^1\) In other words, the risk of death for men on continuous ADT was based on the background mortality rate, before adjusting for excess risk of death associated with CVD and/or hip fracture described in Sections 3.5.2.1 to 3.5.2.3.

3.5.2.4.2 Intermittent ADT

It has been reported that men treated with intermittent ADT are at a lower risk of death due to causes other than prostate cancer compared to those treated on a continuous schedule.\(^1^1,^6^5\) This may include a lower risk of death due to cardiovascular disease as well as hip fractures. Data have not been reported for each of these individually. A further complication is that the present analysis estimates the risk of death associated with each of these comorbidities indirectly based on the risk of developing CVD or experiencing a hip fracture for each treatment arm (continuous ADT and intermittent ADT). Calais da Silva et al. reported the HR for death due to causes other than CVD or prostate cancer of 1.42 (95% CI 0.83 - 2.47); this may include hip fracture as a cause of death. Crook et al. reported no statistical difference in the number of hip fractures for intermittent ADT compared to continuous ADT in men with PSA progression (without metastatic disease) after radical therapy.\(^6^5\) This suggests that there is a lower risk of death associated with intermittent ADT for other causes of death outside of CVD and/or hip fracture.

While there is no difference in OS for intermittent ADT versus continuous ADT, these reported differences in risk of death due to cancer versus other causes are important in the present analysis. This is because death is being predicted based on patients’ health state and history. If the difference in the risk of non-prostate cancer death were not captured,
then the model would over-estimate mortality associated with intermittent ADT. This is because the risk of death due to prostate cancer after progression to hormone refractory disease is assumed to be the same in both arms. Therefore PFS indirectly predicts cancer-specific mortality in the model. Since the risk of progression is higher for intermittent ADT, the probability of death while the disease is stable must be lower if there is no difference in OS as demonstrated in clinical trials.11,65

In the absence of additional data to appropriately capture differences in the risk of death due to causes other than hip fracture and CVD, the data from the trial by Calais da Silva et al. was used as a proxy.11 Therefore the model assumes that the HR for death for men with stable disease and no comorbid conditions in the intermittent arm is 1.42 (95% CI 0.83 - 2.47). The uncertainty around this estimate was captured by using a distribution based on the reported 95% CIs, which captures the possibility that there is no difference between the two treatment arms.

In order to ensure that the difference in OS estimated in the model was similar to what was seen in the trial, the predicted survival curves were compared. The OS rate for each arm in the model was estimated from median survival (from predicted survival curves) and these were then compared as an estimate of the HR for OS. This estimate of the HR from the model was compared to the HR for OS that was reported by Calais da Silva et al. to ensure consistency with the trial data.11

3.5.3 Prostate Cancer-Specific Mortality

Patients diagnosed with prostate cancer also are at increased risk of death due to their disease. The probability of survival is dependent on the stage of disease, especially if patients develop hormone-refractory disease. In the absence of specific data to reflect the probability of death post progression to hormone-refractory disease for the population reflected in the present analysis, several assumptions were made.

Firstly, to estimate the risk of prostate cancer-specific death for patients with metastatic disease versus those with stage III/IV M0 disease, a weighted monthly survival rate was
calculated from 10-year (50% weighting) and 15-year (50% weighting) rates from a study by Johansson et al.\textsuperscript{85} The reported 10-year and 15-year corrected survival rates (prostate cancer as the underlying cause of death) for patients with stage T3/T4 disease were 65.7% (95% CI 56.5% - 74.8%) and 56.5% (95% CI 44.6% - 68.4%), respectively. Similarly, 10-year and 15-year survival rates for patients with metastatic disease were reported as 8.5% (95% CI 3.2% - 11.8%) and 5.7% (95% CI -0.1% - 11.5%), respectively. To reflect the population in the model, the overall prostate cancer-specific mortality rate used to estimate transition probabilities was also weighted by the proportion of patients with metastatic versus locally advanced disease at the start of the model (31% metastatic; 69% non-metastatic with stage T3/T4 disease). Because patients included in the Johansson et al. study were treated hormonally with predominantly estrogen or estramustine, not combined ADT, this method assumes similar efficacy between these two treatment options.\textsuperscript{29,30} The estimated monthly rate of prostate cancer-specific death was converted to a monthly probability using Equation 2.

The present analysis assumes that patients who die from prostate cancer must first progress to hormone-refractory disease. That is, patients with hormone-refractory disease are assumed to die as a result of their disease. Since the data from Johansson et al. was reported from the time of diagnosis, not from the time of disease progression, it was necessary to adjust the prostate cancer specific survival rate to reflect the probability of death post progression. This method uses the underlying probability of prostate cancer-specific survival with the associated uncertainty as the basis for predicting death post progression.

The probability of death from castrate metastasis used by Ito et al. was 50% per year (approximately 5.8% per month).\textsuperscript{85} This was the starting point for determining what the appropriate multiplier should be and then small adjustments were made to reflect the published curve from the Calais da Silva et al. trial that included the population that was the basis of the present analysis.\textsuperscript{11} Using this method, a multiplier of 7.5 was determined to be
a good estimate, resulting in an overall probability of death post progression to hormone-refractory disease of approximately 5.9% per month.

### 3.5.4 Adverse Effects of ADT

The model considers three key effects of androgen deprivation therapy that are expected to be affected by the choice of an intermittent strategy compared to a continuous strategy: SDF, CVD, and hip fractures due to decreased BMD caused by ADT. In the absence of a strong body of evidence, several assumptions were made in order to reflect these events based on data collected from various published sources.

#### 3.5.4.1 Sexual dysfunction

Rates of de novo SDF for individuals were estimated from data reported in the trial by Calais Da Silva et al. In the trial, more men in the continuous arm reported that sexual activity was decreased than in the intermittent arm. At 15 months, 28% of men in the intermittent arm reported sexual activity compared to 10% of men in the continuous arm. Using the proportion of men who reported being sexually active at registration as a proxy for SDF at baseline, a rate of SDF was estimated for each arm of the model. Transition probabilities were then estimated using an exponential function and assuming a constant rate. Probabilities were assumed to follow a beta distribution estimated using the methods previously described.

#### 3.5.4.2 Cardiovascular disease

In the Calais da Silva et al. trial 10.3% of patients in the continuous arm reported having CVD at baseline and 16.7% died of cardiovascular causes. While this strongly suggests that there are cases of incident CVD in the continuous arm, data were not available to estimate probabilities. In addition, a similar result was not reported in the intermittent arm (17.2% with CVD at baseline compared to 13.1% cardiovascular deaths). The HR (continuous versus intermittent) for cardiovascular death reported by Calais da Silva et al. was 1.32 (95% CI 0.87 – 1.99) after adjusting for the higher proportion of patients with CVD at baseline.11 Due
to the data gaps in the literature, it was necessary to make some assumptions about rates of incident CVD in the model.

The probability of developing incident CVD in the intermittent arm was based on results from Keating et al. Based on the relatively short on-treatment phase in the intermittent arm and the lack of data comparing CVD in men on intermittent ADT to individuals who do not receive ADT, the probability of developing incident CVD in the intermittent arm of the model was based on rates of incident coronary heart disease (which included men with MI) reported by Keating et al. for men who received no ADT (61.3 per 1000 person-years). This served as a proxy for rates of developing CVD in the absence of a standard definition between trials.

For patients in the continuous arm, it was assumed that the adjusted HR for cardiac death of 1.32 reported by Calais Da Silva et al. reflects the difference in the probability of developing incident coronary heart disease (CHD). This assumption may underestimate the relative risk of developing incident CHD: however, no additional data was provided for cardiovascular outcomes in the study. Given that this was the best available evidence comparing intermittent ADT and continuous ADT in a population with advanced disease it was used as a proxy. A log normal distribution was used to reflect uncertainty in this parameter.

It should be noted that Keating et al. reported a HR of 1.16 (95% CI 1.10 to 1.21) for incident CHD for men on ADT compared to those not treated with ADT. Because no data were available from trials comparing intermittent to continuous ADT, it was felt that assuming a statistically significant difference in incident CVD (as reported by Keating et al.) in the model may overestimate the cardiovascular benefits. Given the conflicting data in the literature regarding the effects of ADT on cardiovascular outcomes, this approach was considered more conservative.
3.5.4.3 Hip Fractures

As previously described, there is evidence to suggest that BMD loss is attenuated for patients treated with intermittent ADT. Given that low BMD is associated with increased fracture risk, the model accounts for changes in BMD over time in each group in order to estimate differences in hip fracture incidence between intermittent and continuous ADT.

In the absence of robust data comparing the effects of intermittent ADT to continuous ADT on bone, it was necessary to make some assumptions. The amount of BMD decline (g/cm²) each month was estimated from data used in a recently published cost-effectiveness analysis of fracture prevention in men with prostate cancer treated with ADT. During ADT treatment it was assumed that BMD declined by 0.019 g/cm² per year compared to a decline of 0.004 g/cm² for the time spent off therapy. Off therapy included the time during which patients had hormone-refractory disease in the model and were therefore no longer receiving ADT. Normal distributions were used for the change in BMD over time while on ADT and off ADT.

BMD values sampled for each simulation in the model were then used to calculate a T-Score at the individual level for each cycle using a published reference mean and standard deviation according to the following formula: T-Score = BMD – Reference BMD/Standard deviation of the reference mean. Using a lookup table with 10-year fracture risk data (converted to monthly probabilities) published by Kanis et al. by age and T-Score, the model predicts the total number of hip fractures for each arm of the model. The model tracks the total number of hip fractures as well as the age at which each fracture occurs. In the model, patients who experience one fracture are at increased risk of subsequent fracture. This excess risk was modeled by age using log normal distributions with means and standard deviations based on a meta-analysis of relative risk by Kanis et al. The predicted incidence of hip fracture in the continuous arm was compared to published studies to assess the validity of the model. Since fracture data for men on intermittent ADT were not available, it was not possible to directly validate the predictions. Therefore, the assumption was made that the predicted number of hip fractures in the intermittent arm would be
lower than those of men receiving continuous ADT but higher than men not receiving ADT based on the relative fracture rates reported in studies comparing no ADT to ADT.

3.5.5 Quality of Life

Utilities were used to reflect the impact of prostate cancer as well as adverse effects of ADT treatment on overall quality of life. Using these weights, the model calculates quality-adjusted survival for intermittent ADT compared to continuous ADT. All utilities were taken from published sources and are summarized in Table 3.

Utilities for stable prostate cancer were estimated using a weighted average from data published by Krahn et al. to reflect differences in the metastatic status of patients. Standard gamble utilities collected from the Patient Oriented Prostate Utility scale (PORPUS) with mean utilities of 0.86 for those without metastatic disease compared to 0.85 for those with metastatic disease. Assuming 31% of patients in the model were metastatic at baseline, a weighted utility of 0.857 was used to reflect quality of life in the stable disease state for our mixed cohort. Utilities for hormone-refractory disease were taken from baseline measures in a study mapping EQ-5D scores in metastatic hormone-refractory prostate cancer patients to other quality of life instruments.

Prostate cancer utilities were combined with utilities for other conditions using either multiplicative methods or applying decrements. In the case of CVD, utility scores were estimated using data for patients with a Charlson Comorbidity scale score of \(< 2\) from the study by Krahn et al. as a proxy. The utility scores for CVD were then combined with prostate cancer state utilities multiplicatively in order to estimate the utility score for patients in combined health states (e.g. hormone refractory disease and CVD). This method may underestimate utility scores since the patients in the study by Krahn et al. who had a Charlson Comorbidity scale score of \(< 2\) also had prostate cancer. Since utility scores for patients with Charlson Comorbidity scales scores of \(< 2\) were not stratified by the patients’ prostate cancer specific state, it was necessary to make an assumption. Similarly, for hip fracture utilities associated with the first year following hip fracture as well as
subsequent years, a multiplicative approach was used to capture additional effects on quality of life (i.e. for combined health states). Utilities for hip fracture were taken from values used by Ito et al. in their analysis.\textsuperscript{76}

For those with SDF, a utility decrement of 0.04 was subsequently subtracted.\textsuperscript{89} A decrement was used in this case because it was reported as the adjusted difference between patients in the best and worst quartiles of UCLA Prostate Cancer Index Subscale score. For patients on treatment, a further decrement of 0.02 was applied based on data suggesting that being on ADT therapy is associated with lower utilities.\textsuperscript{89} In the study by Krahn et al. the utility difference for men on ADT versus those not on ADT was 0.02 to 0.03. Given that some of the quality of life effects of ADT may be captured in the utility decrement associated with SDF, 0.02 was used in the model. A multiplicative approach was felt to overestimate the effect of ADT therapy on quality of life and lead to too much double counting since the effects of some of the adverse effects of ADT are already captured by combining utilities for key AEs associated with ADT (CVD, hip fracture). The difference of 0.02 may be due to other side effects of ADT therapy such as hot flashes, which are not captured directly in the present model. Calais Da Silva et al. reported that the incidence of hot flashes, gynaecomastia, and headaches were lower in patients treated with intermittent therapy compared to continuous ADT.\textsuperscript{67} The utility of death was assumed to be 0.

### Table 3. Quality of Life Input Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(Expected) Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility for stable prostate cancer (weighted)</td>
<td>0.857</td>
<td>Beta</td>
<td>Assumption, 89</td>
</tr>
<tr>
<td>Utility for hormone refractory prostate cancer</td>
<td>0.635</td>
<td>Beta</td>
<td>90</td>
</tr>
<tr>
<td>Utility CVD</td>
<td>0.870</td>
<td>NA</td>
<td>Assumption, 89</td>
</tr>
<tr>
<td>Utility for hip fracture first year</td>
<td>0.792</td>
<td>NA</td>
<td>76</td>
</tr>
<tr>
<td>Utility for hip subsequent years</td>
<td>0.813</td>
<td>NA</td>
<td>76</td>
</tr>
<tr>
<td>Utility decrement for SDF</td>
<td>0.040</td>
<td>NA</td>
<td>89</td>
</tr>
<tr>
<td>Utility decrement during ADT therapy</td>
<td>0.020</td>
<td>NA</td>
<td>Assumption, 89</td>
</tr>
</tbody>
</table>
3.5.6 Costs
Costs used in the model were collected from published and unpublished studies and adapted for this analysis. The methods used to define costs are described in the following sections. Only direct medical costs were considered to reflect a Ministry of Health perspective. Where required, costs were adjusted to 2011 CAD. All costs and adjustment factors used in the model are summarized in Table 5.

3.5.6.1 Drug Costs
Drug costs were estimated based on prices listed in the Ontario Drug Benefit Formulary. Unit costs were $1.61 per 50 mg tablet of bicalutamide and $1,087.82 for a 9.45 mg depot of buserelin. As described previously, it was assumed that patients received 9.45 mg of buserelin every 3 months and 50 mg of buserelin daily. An 8% markup was added to unit costs based on what is allowable under the drug plan. In addition, dispensing fees of $7.00 less a co-payment of $6.11 were included to reflect the costs to the Ministry of Health for these therapies. Drug costs were calculated for 100 days assuming that buserelin is dispensed once every 3 months (90 days) and bicalutamide is dispensed every 30 days. This was done so that the cost could be added to the mean cost of stable disease calculated in section 3.5.6.3 for patients in the “stable on treatment” state. The total estimated drug cost per 100 days was $1,483.22 assuming 100% compliance.

3.5.6.2 Monitoring Costs
For men on intermittent ADT, an additional cost for PSA tests each month during the off-treatment period was applied. This is because while patients may not be taking hormone therapy during the off-treatment phase, additional monitoring is required to determine when to re-initiate therapy. The cost of a PSA test was assumed to be $16.49 (2011 CAD) based on a study by Krahn et al. that included a cost of a PSA test of $12.00 from a Toronto hospital in 1995 Canadian dollars.
3.5.6.3 Prostate Cancer Health State Costs

The costs for health states associated with prostate cancer were estimated from an unpublished study evaluating the direct health costs for prostate cancer using data from Ontario, Canada. In the study, men with an initial diagnosis of prostate cancer in 1993, 1994, 1997, 1998, 2001, and 2002 were identified in the Ontario Cancer Registry. Patients’ observation times were allocated to 11 prostate cancer-specific Markov states. Clinic chart data were linked to data from administrative databases to estimate resource use for the period of time spent in each health state and costs were assigned. The authors reported the mean cost per 100 days for eleven prostate cancer specific health states including: patients with non-metastatic prostate cancer receiving hormone therapy, patients who progress to hormone refractory non-metastatic disease, patients with stable metastatic disease (with or without hormone therapy), patients with metastatic disease who have progressed or become refractory to therapy, and patients in the last 180 days of life (death state). A regression analysis was performed to measure predictors of costs and a formula for predicting the costs based on various patient characteristics was provided. Predictors of cost included age, number of ambulatory diagnostic groups assigned, PSA level at diagnosis, stage of disease at diagnosis, Gleason score, and health state.

To estimate the mean cost for prostate cancer-specific states from the unpublished study relevant for the model, a regression equation provided by the authors was used. The values used for parameters in the regression equation were selected based on the characteristics of the population in the model. Specifically, it was assumed that patients were 72.6 years old with PSA levels of > 20 ng/ml and a Gleason score of 7 at diagnosis. The costs for each of the health states calculated using the regression equation are summarized in Table 4 by metastatic status at diagnosis. This is because the model included both patients with stage T3/4 disease as well as M1 disease.
Table 4. Predicted Mean Total Costs per 100 days by Health State (Unpublished)\textsuperscript{94}

<table>
<thead>
<tr>
<th>Health State</th>
<th>Predicted Mean Cost (Standard Error) in 2008 CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone treated localized prostate cancer</td>
<td></td>
</tr>
<tr>
<td>M0 at diagnosis</td>
<td>$4,052.14 ($13,199.85)</td>
</tr>
<tr>
<td>Metastatic prostate cancer stable</td>
<td></td>
</tr>
<tr>
<td>M1 at diagnosis</td>
<td>$4,872.69 ($16,612.41)</td>
</tr>
<tr>
<td>Hormone treated refractory/progression localized prostate cancer</td>
<td></td>
</tr>
<tr>
<td>M0 at diagnosis</td>
<td>$2,701.54 ($8,808.42)</td>
</tr>
<tr>
<td>M1 at diagnosis</td>
<td>$5,222.41 ($17,820.70)</td>
</tr>
<tr>
<td>Death (last 180 days)</td>
<td></td>
</tr>
<tr>
<td>M0 at diagnosis</td>
<td>$13,217.15 ($43,050.07)</td>
</tr>
<tr>
<td>M1 at diagnosis</td>
<td>$14,206.23 ($48,424.74)</td>
</tr>
</tbody>
</table>

In the model, costs for each prostate cancer health state (stable disease on treatment, stable disease off treatment, hormone refractory prostate cancer, and death) were calculated based on a weighted average of the state specific costs in Table 4 adjusted to 2011 CAD. The weighted average was determined based on the proportion of patients who were assumed to be metastatic at model entry (See Table 2). Note that for the death state only a one-time cost was applied based on the last 6 months of life.

Since costs for patients with metastatic stable disease were not reported separately for patients on hormone therapy versus those not receiving hormone therapy in the study\textsuperscript{94}, the proportion of costs attributed to drugs was excluded from the mean cost. The adjusted mean total cost was calculated using the following equation:

\[
\text{AdjMTC/100d} = \frac{\text{MTC health state/100d}}{1-\frac{\text{MTC drugs/100d}}{\text{MTC health state/100d}}}
\]

(Equation 3)

\text{AdjMTC} = \text{Adjusted mean total cost}
\text{d= days}
\text{MTC= Mean total cost}

Similarly, for patients with non-metastatic disease treated with hormone therapy, the proportion of total health state costs from drugs was excluded so that the cost of intermittent therapy could be calculated in a manner consistent to continuous therapy. For patients in this state, drug costs represented 39.4\% of the total health state cost.\textsuperscript{94} Though
the cost of drugs reported for patients in this health state could include drugs other than hormone therapy, it is likely that the impact of excluding these costs is low. As demonstrated in section 3.5.6.1, the estimated cost of hormone therapy for 100 days is approximately $1,483 (2011 CAD) compared to a mean of $1,377 in 2008 CAD ($1,449 in 2011 CAD) reported for the overall population receiving hormone therapy in the unpublished study. This suggests that the majority of the drug costs for patients in this state are the costs of hormone therapy itself. Similarly, for patients treated with radical prostatectomy (which is intended to be curative), drug costs in the unpublished study were reported to be only $142 ($149 in 2011 CAD). \(^9^4\) Again, this suggests that drug costs outside of hormone therapy itself are low.

In the present analysis, the cost of patients with stable disease while off therapy was estimated using a weighted average of the adjusted mean cost for patients with non-metastatic disease (61%) and those with metastatic disease (39%) based on the population simulated in the model. The cost of the stable health state for patients on therapy in the model was calculated as the sum of the weighted average cost, plus the cost per 100 days of drugs calculated in section 3.5.6.1.

\[
\text{WA cost stable off Tx/100 d} = (\text{AdjMTC NM/100d x ProNM}) + (\text{AdjMTC M/100d x PropM})
\]

(Equation 4)

\[
\text{WA cost stable on Tx/100d} = \text{WA cost stable disease off T/100dx} + \text{cost of drugs/100d}
\]

(Equation 5)

WA= weighted average
d=days
Tx = treatment
AdjMTC = Adjusted mean total cost (see Equation 3)
PropNM = Proportion of model population non metastatic
PropM = Proportion of model population metastatic

Similarly, for patients in the progressed or hormone-refractory health state, a weighted average of the mean total cost of the progressed health states in Table 2 was used.\(^9^4\) Here,
no adjustment was made to exclude drug costs as it was assumed drugs taken following progression while on hormone therapy would not include the cost of these agents. In addition, a one-time cost of death was applied based on the cost of the last six months of life as reflected in the unpublished study.

Costs for all prostate cancer specific health states, with the exception of the death state, were converted from cost per 100 days (as calculated from the regression equation) to monthly costs assuming each month is 30 days. All costs were reported in 2008 Canadian dollars (CAD)\(^9\) and were adjusted to 2011 dollars using the Consumer Price Index (CPI).\(^\text{95}\)

### 3.5.6.4 Cost of Sexual Dysfunction

The cost SDF in the model was estimated as the cost of two visits to an urologist per year. The cost per visit, $26.00, was taken from the Ontario Schedule of Benefits assuming a partial assessment is charged.\(^\text{96}\) While various treatment options may exist depending on the definition of SDF being used, an assumption was made that most of the costs associated with treatments for SDF would not be covered by the Ministry of Health. This is because most of the therapies for SDF (sildenafil, tadalafil, and vardenafil) are not listed on the Ontario Drug Benefit formulary.\(^\text{92}\)

### 3.5.6.5 Cost of Cardiovascular Disease

An annual average cost of CVD was included in the model for all prostate cancer states that included comorbid CVD. The average cost was taken from a Canadian study by Smolderen et al. which provided an estimate of medication costs and hospitalization costs for patients with various forms of CVD.\(^\text{97}\) The present analysis assumes that the average cost of drugs ($1,593) and hospitalizations ($1,832) for patients with coronary artery disease reported by Smolderen et al. represents the cost of comorbid CVD. Costs were adjusted from 2006 values to 2011 CAD using CPI.\(^\text{95}\) Annual costs added to determine the overall annual cost of CVD and converted to monthly costs to reflect the cycle length in the model.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>(Expected) Value*</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Costs (including 8% markup, $7.00 dispensing fee and $6.11 co-pay per dispense)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicalutamide 50 mg/day (cost per 100 days)</td>
<td>$176.85</td>
<td>NA</td>
<td>80,92</td>
</tr>
<tr>
<td>Buserelin 9.45 mg/3 months (cost per 100 days)</td>
<td>$1,306.37</td>
<td>NA</td>
<td>80,92</td>
</tr>
<tr>
<td>Monitoring Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPI adjustment factor (1995 to 2011 CAD)</td>
<td>1.37</td>
<td>NA</td>
<td>95</td>
</tr>
<tr>
<td>Prostate specific antigen cost (1995 CAD)</td>
<td>$12.00</td>
<td>Gamma</td>
<td>93</td>
</tr>
<tr>
<td>Prostate Cancer Disease State Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPI adjustment factor (2008 to 2011 CAD)</td>
<td>1.05</td>
<td>NA</td>
<td>95</td>
</tr>
<tr>
<td>Stable disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Metastatic (per 100 days; 2008 CAD)</td>
<td>$4,052.14 (SE $13,199.85)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Metastatic (per 100 days; 2008 CAD)</td>
<td>$4,872.69 (SE $16,612.41)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Proportion of stable disease state costs that are drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>19.60%</td>
<td>NA</td>
<td>94</td>
</tr>
<tr>
<td>Non Metastatic</td>
<td>39.40%</td>
<td>NA</td>
<td>94</td>
</tr>
<tr>
<td>Total adjusted cost per 100 days in stable off treatment state (weighted)</td>
<td>calculated*</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Total cost per 100 days in stable on treatment state (weighted)</td>
<td>calculated†</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Cost of progression/hormone refractory state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Metastatic (per 100 days; 2008 CAD)</td>
<td>$2,701.54 (SE $8,808.42)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Metastatic (per 100 days; 2008 CAD)</td>
<td>$5,222.41 (SE $17,820.70)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Total cost per 100 days in progressed/refractory state (weighted)</td>
<td>calculated‡</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Cost of death state</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Metastatic (per 100 days; 2008 CAD)</td>
<td>$13,217.15 (SE $43,050.07)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Metastatic (per 100 days; 2008 CAD)</td>
<td>$14,206.23 (SE $48,424.74)</td>
<td>Gamma</td>
<td>94</td>
</tr>
<tr>
<td>Total one-time cost of Death state (weighted)</td>
<td>calculated¥</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Cost of CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPI adjustment factor 2006 to 2011 CAD</td>
<td>1.10</td>
<td>NA</td>
<td>95</td>
</tr>
<tr>
<td>Annual cost of drugs (2006 CAD)</td>
<td>$1,593.00 (SD $1,593.00)</td>
<td>Gamma</td>
<td>Assumption,97</td>
</tr>
<tr>
<td>Annual cost of hospitalizations (2006 CAD)</td>
<td>$1,823.00 (SD $1,823.00)</td>
<td>Gamma</td>
<td>Assumption,97</td>
</tr>
<tr>
<td>Total cost of CVD by month</td>
<td>calculated¥</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Cost of Hip Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPI adjustment factor 1997 CAD to 2011 CAD</td>
<td>1.34</td>
<td>NA</td>
<td>95</td>
</tr>
<tr>
<td>Cost of hip fracture in first year (1997 CAD)</td>
<td>$22,700 (95% CI $18,274–$27,126)</td>
<td>Gamma</td>
<td>98</td>
</tr>
<tr>
<td>Total monthly cost of hip fracture in first year</td>
<td>calculated¥</td>
<td>NA</td>
<td>Assumption</td>
</tr>
<tr>
<td>Cost of SDF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per month</td>
<td>calculated¶</td>
<td>NA</td>
<td>Assumption,96</td>
</tr>
</tbody>
</table>

Numbers not exact due to rounding. Weighted = weighted by proportion metastatic/non-metastatic. SD = standard deviation, CAD = Canadian Dollars, CPI = Consumer Price Index.

* Stable off treatment cost is calculated based on the sampled health state costs by metastatic status, less drug costs, weighted by the proportion of patients metastatic and non-metastatic at model entry in Table 1 (31% metastatic, 69% non-metastatic) and adjusted for inflation.

† Stable on treatment cost is calculated as the stable off treatment cost plus the cost of drugs shown.

‡ Calculated based on the sampled health state cost by metastatic status, weighted by the proportion of patients metastatic and non-metastatic at model entry in Table 1 (31% metastatic, 69% non-metastatic) and adjusted for inflation.

¥ Calculated based on reported cost/100 days in health state times 180 days based on definition of death state used in the unpublished study as the last 180 days before death. Cost is a weighted value based on the proportion of patients metastatic and non-metastatic and adjusted for inflation.

¶ Calculated as the cost of two partial assessments by a urologist per year [(2 x $26.00)/12 months per year]
3.5.6.6 Cost of Hip Fracture

The cost in the first year following a hip fracture was taken from a Canadian study by Wiktorowicz et al.\textsuperscript{98} The authors reported that the average cost of therapy in the first 12 months following a hip fracture for men was $22,770 (95% CI $18,274–$27,126) in 1997 CAD. This includes patients who survived the full year as well as those who died earlier than 12 months following the fracture event. Costs in the study were calculated based on resource utilization data and unit costs from Ontario. Resource use categories included were initial hospitalization, rehospitalisation, rehabilitation, long term care, home care and informal care. While the authors included some costs which may reflect a societal perspective (e.g. informal caregiver time, some long-term care costs), it was assumed that this was a small portion of the overall costs and would not have a significant impact on the results of the present analysis which is intended to reflect a Ministry of Health perspective. In their study, Wiktorowicz et al. reported that 338 of 504 patients were returned to the community and only 3% of the total cost for these patients was attributed to informal care.\textsuperscript{98} For patients in long-term care facilities, the biggest cost was the cost of long-term care itself. In Ontario, long-term care is subsidized by the province on a cost-sharing basis depending on the individual's ability to pay. Therefore, it was felt reasonable to assume that the Ministry incurs a significant portion of any long-term care costs. This would indicate that the majority of the costs included in the study are paid directly by the Ministry of Health.

For the purposes of the present analysis, if a hip fracture occurred, only the cost of the first year following the event was included. It was assumed the cost in subsequent years would be captured in the prostate cancer health state costs. Costs were adjusted to 2011 dollars using CPI.\textsuperscript{95}

3.6 Scenario Analyses

Scenario analyses were conducted to evaluate differences in outcomes based on various patient populations. All scenario analyses were simulated using 3,000 samples and 10,000
trials. All scenario analyses are summarized in Table 6 along with key parameters that were changed.

3.6.1 Only Patients with Metastatic Disease

The first scenario included patients with metastatic disease only at model entry. Men with metastatic disease are expected to have lower OS and PFS and therefore various parameters would change from the baseline analysis. In the model, various inputs were calculated as a weighted average based on metastatic status at model. These included prostate cancer-specific mortality rates and progression rates as well as prostate cancer health state specific utilities and costs. Therefore, by changing the proportion of patients with metastatic disease to 100%, all of these input parameters were also adjusted.

In this scenario analysis, the probability of death was assumed to be constant over time based on the probability of death due to prostate cancer for patients with metastatic disease plus the background probability of death from life tables. This method was used because there was a lack of data comparing PFS for intermittent versus continuous ADT by metastatic status but there were data comparing OS. Since the probability of death after progression to hormone-refractory disease is higher in the base case analysis, differences in OS are indirectly captured based on differences in the rate of progression. By using a time-dependent probability of death for patients with metastatic disease on continuous ADT the HR for OS for intermittent versus continuous ADT from Calais da Silva et al. could be used to capture differences in survival in the model. The HR for OS used was 0.794 (95% CI 0.562 - 1.111), calculated as the inverse of the HR for OS for continuous vs intermittent ADT in patients with metastatic disease at study entry. A normal distribution for the log HR was used to reflect uncertainty. Again, PFS was not reported by metastatic status by Calais da Silva et al. As no alternative data source was identified, it was assumed that the HR for PFS was the same as the base case analysis.
3.6.2 No Prevalent Sexual Dysfunction at Model Entry

In the second scenario, the cost-effectiveness of intermittent ADT relative to continuous ADT was evaluated for a subgroup of the base case population that did not have prevalent SDF. In this case, all transition probabilities were assumed to be the same as in the base case analysis. Only the initial cohort was redistributed so that no patients entered the model with SDF.

3.6.3 Younger Men with No Prevalent Comorbidities at Model Entry

A third analysis evaluated the incremental cost per QALM based on a subpopulation of younger men (age 65 years) without existing SDF or CVD. The population was redistributed so that no patients entering the model had prevalent SDF or CVD. In addition, mean BMD at model entry was adjusted to those of men aged 60-69 (0.788 ± 0.135). It was assumed that the probability of developing de novo SDF remained the same as in the base case analysis. This is because of a lack of data reporting on rates of developing SDF by age and ADT status. In addition, this assumes that the rates of de novo SDF from the clinical study by Calais da Silva et al. include both underlying risk of developing SDF as well as SDF caused by ADT. Similarly, data reporting rates of developing CVD by age and ADT status were not identified. The base line rate of developing incident CVD was also taken from a study with a population that included 24% of men aged 66 years to 69 years. Therefore, the probability of developing de novo CVD was also assumed to be the same as in the base case analysis.
### Table 6. Summary of Scenario Analyses

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Input Parameters Changed Directly</th>
<th>Input Parameters Changed Indirectly*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 1: All patients metastatic at model entry</strong></td>
<td></td>
<td>All parameters weighted by metastatic status including: prostate cancer specific mortality, probability of progression, prostate cancer health state costs, utilities of health states</td>
</tr>
<tr>
<td>No patients with stage T3/T4 disease</td>
<td>Proportion of patients with metastatic disease at entry = 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probability of death constant over time = prostate cancer specific mortality + background probability of death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR for OS INT vs CONT ADT = 0.794 (95% CI 0.562 - 1.111)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All parameters weighted by metastatic status including: prostate cancer specific mortality, probability of progression, prostate cancer health state costs, utilities of health states</td>
<td></td>
</tr>
<tr>
<td><strong>Scenario 2: No prevalent SDF; other characteristics same as base case</strong></td>
<td>Cohort distributed as follows at entry:</td>
<td>None</td>
</tr>
<tr>
<td>No prevalent SDF at entry, all other characteristics assumed to be the same as base case</td>
<td>Stable on Tx= 89.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus SDF = 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus CVD = 10.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus CVD &amp;SDF = 0%</td>
<td></td>
</tr>
<tr>
<td><strong>Scenario 3: Younger men with no prevalent SDF and no prevalent CVD</strong></td>
<td>Mean age = 65</td>
<td>Background mortality rates</td>
</tr>
<tr>
<td>No prevalent SDF or CVD at model entry and younger men; probability of developing de novo SDF or CVD same as base case</td>
<td>Mean baseline BMD = 0.788 (+ 0.135)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohort distributed as follows at entry:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx= 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus SDF = 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus CVD = 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stable on Tx plus CVD &amp;SDF = 0%</td>
<td></td>
</tr>
</tbody>
</table>

SDF = Sexual Dysfunction, CVD = Cardiovascular Disease, BMD = Bone Mineral Density Tx = Treatment
*Parameters that change indirectly are those which reference parameters changed directly for scenario analyses.

### 3.7 Model Outcomes

The primary outcome measure in the present analysis is the incremental cost-effectiveness ratio for intermittent versus continuous ADT based on the predicted mean total costs and QALMs for each intervention (discounted). Additional outcome measures include: mean total LMs (discounted), mean total costs undiscounted, mean total QALMs undiscounted, mean total LMs undiscounted, mean total time off hormone therapy, mean proportion of patients with cardiovascular disease, mean number of hip fractures per patient, mean time without SDF and the mean proportion of patients with SDF.

Optimality curves based on net health benefits (NHBs) were also developed. NHBs are calculated as the difference between the mean effectiveness of an intervention (µEi) and the mean cost of the intervention (µCi) divided by the willingness to pay threshold (λ) [i.e. NHB = µEi – (µCi/λ)]. In other words, the difference between the intervention’s effectiveness and the minimum health effect that is expected in return for an investment.
equal to the cost associated with that intervention. Similarly, the incremental NHB of one intervention compared to another intervention is calculated as:

\[ \text{Incremental NHB} = (\mu_{E2} - \mu_{E1}) - (\frac{(\mu_{C2} - \mu_{C1})}{\lambda}) \]

This can be interpreted as the difference in NHBs between two programs compared to the minimum difference in health effects that are expected in return for the additional investment associated with one program over the other. If the incremental NHB is greater than zero, then the intervention is considered cost-effective and should be accepted or implemented. That is, the incremental NHBs of the intervention are greater than the minimum additional NHBs expected for the additional cost of that program. Conversely, if the incremental NHB is less than zero, then the intervention does not provide the additional effects expected based on the additional costs required to implement that intervention. The willingness to pay threshold used was $50,000/QALY or $4,167 per QALM.
4 Model Validation

4.1 Overall Survival

The OS curves predicted from the simulation model in the base case analysis are presented in Figure 2 and Figure 3 for continuous and intermittent ADT, respectively. The median survival estimate for men receiving continuous ADT was approximately 55 months (Figure 2). This was similar to the estimated median survival of approximately 60 months for continuous ADT from published Kaplan-Meier curves in the study by Calais da Silva et al. which is reflective of the population included in the present analysis. Given that various different sources were used to calculate OS in the model based on co-morbid conditions and prior events, this similarity to a published curve measured directly in a clinical trial suggests the model’s survival predictions are appropriate. The median survival times for intermittent ADT (Figure 3) predicted in the model (approximately 52 months) were similar, in line with data from the literature showing no difference in OS compared to continuous ADT. The model predicted values were also similar to other published data such as Miller et al. who reported median OS times of 51.4 months and 53.8 months for intermittent and continuous therapy, respectively. The population characteristics were not well described therefore it was difficult to compare the model to these data as there may have been a higher proportion of patients with metastatic disease in the trial.

The total estimated mean survival in the model for continuous ADT was also similar to estimates published by Bayoumi et al. in their analysis of various forms of ADT for advanced prostate cancer. For continuous ADT the mean survival predicted in the present analysis was approximately 83.6 months (undiscounted) or 7.0 years compared to estimated survival of 7.54 years (undiscounted) for combined ADT estimated by Bayoumi et al. based on a slightly younger population (65 years of age) with a history of prostate cancer.
Figure 2. Overall Survival Curve in the Base Case Analysis for Continuous ADT from Markov Model

Figure 3. Overall Survival Curve in the Base Case Analysis for Intermittent ADT from Markov Model
When the scenario analysis that included only patients with metastatic disease was performed, the model-predicted median survival was approximately 32 months in the continuous ADT arm (Figure 4). This is similar to reported median OS from studies of patients with metastatic disease by Dijkman et al. (median OS 27.3 months) and Denis et al. (median OS 34.4 months). Median OS by metastatic status estimated from the published Kaplan-Meier curves in the Calais da Silva et al. study were approximately 35 months and 51 months for continuous ADT and intermittent ADT, respectively (HR for continuous versus intermittent ADT of 1.26; 95% CI 0.90 – 1.78) The model-predicted median survival for patients with metastatic disease only in the intermittent ADT arm was approximately 40 months (Figure 5). This is in line with what would be expected based on an estimated mortality rate of 0.022/month in the continuous arm. The expected rate in the intermittent arm is 0.017/month based on HR of 0.79).

**Figure 4. Overall Survival Curve from Scenario Analysis of Patients with metastatic disease for Continuous ADT from Markov Model**

![Overall Survival Curve from Scenario Analysis of Patients with metastatic disease for Continuous ADT from Markov Model](image)
4.2 Progression-Free Survival

Due to differences in the way PFS is reported, it is difficult to compare predicted values to trial data. To ensure the model was appropriately calculating PFS in the continuous ADT arm, the predicted rate of progression (estimated from the PFS curve from the model) was compared to the weighted average survival rate from the two studies used in the model. As shown in Figure 6, the median PFS is approximately 52 – 53 months (at 52 months, 50.36% of patients surviving). This equates to a PFS rate of 1.35% per month based on Equation 1. The weighted average PFS rate estimated from the studies by Johansson et al. and Dijkman et al. was 1.37%, suggesting the model output is consistent with what is expected. 23,85

The PFS curve for intermittent ADT calculated in the base case analysis is presented in Figure 7. The median PFS predicted from the model was approximately 42 – 43 months (at 43 months, 49.64% of patient surviving). Given the hazard ratio for progression of 0.80 (95% CI 0.63 – 1.05) for continuous versus intermittent therapy, the predicted curve is aligned with the expectation that patients would progress more quickly in the intermittent arm. The
Figure 6. Progression-Free Survival Curve in the Base Case Analysis for Continuous ADT from Markov Model

Figure 7. Progression Free Survival Curve in the Base Case Analysis for Intermittent ADT from Markov Model
estimated survival rate from the curve was 0.016 per month for intermittent ADT. Applying a HR of 0.810 to the rate of 0.016 predicted for intermittent ADT results in an estimated survival rate of 0.129 per month for continuous ADT.

The median PFS estimates predicted from the model were somewhat lower than those estimated from Kaplan-Meier curves reported by Calais da Silva et al. This is because the data used to populate the model, including the probability of progression for patients with metastatic disease compared to those with stage T3/T4 disease was taken from various sources. The predicted PFS curve in the continuous arm is, however, consistent with what would be expected based on what has been reported by other authors in patients with advanced disease. For example, Miller et al. reported median PFS of only 16.6 months for patients receiving continuous ADT and 11.5 months for those receiving intermittent ADT. Similarly, other studies have reported PFS of just over one year for continuous ADT (452 days) with patients on intermittent ADT experiencing a longer time to progression (650 days). Others have reported a 3-year risk of progression to androgen independent disease in patients receiving continuous ADT of 38.9% (+ 11.2%) compared to 7.0% (+ 4.8%) for intermittent ADT. Due to differences in patient populations and definitions of progression, it is difficult to compare; however, the predicted median PFS is within the range of what has been reported in the literature.

In the scenario analysis which evaluated patients with metastatic disease only, the median PFS estimates for continuous (Figure 8) and intermittent ADT (Figure 9) were approximately 21 and 17 months, respectively. This is in line with what would be expected based on input parameters used in the analysis. For continuous ADT, PFS survival rates in the model were derived from the study by Dijkman et al. which reported median PFS of 21.2 months for men receiving CAB. The rate of progression based on 50.3% of patients surviving at 17 months in the intermittent ADT arm equates to a rate of progression of 0.041 per month. Given that the HR for intermittent ADT versus continuous ADT used in the model was 1.24, the predicted median survival is in line with expected values given a rate of progression of 0.033 per month in the continuous ADT arm (0.033 x 1.24 = 0.041). Only one study was
Figure 8. Progression-Free Survival Curve from Scenario Analysis of Patients with metastatic disease for Continuous ADT from Markov Model

Figure 9. Progression-Free Survival Curve from Scenario Analysis of Patients with metastatic disease for Intermittent ADT from Markov Model
identified that reported median PFS data for intermittent versus continuous ADT in patients with metastatic disease (though no HRs were reported).\textsuperscript{14} Median PFS was reported to be 620 days for patients receiving continuous ADT (approximately 20 months) and 425 days (approximately 14 months) for intermittent ADT. This suggests that the estimates in the present model are within the range of what has been seen in clinical trials.

### 4.3 Sexual Dysfunction

The model predicted that, of patients treated with intermittent ADT, a mean proportion of 0.725 (72.5\%) would have SDF (including both incident cases as well as patients with SDF at model entry) based on a lifetime horizon. Of patients treated with continuous ADT, the predicted mean proportion of patients with SDF was 0.870 (87.0\%). This suggests that the corresponding proportion of patients without SDF would be 27.5\% and 13.0\% for intermittent and continuous ADT, respectively. Calais da Silva et al. reported that at 15 months after randomization 28\% of men in the intermittent arm reported sexual activity compared to 10\% in the continuous arm.\textsuperscript{11} Baseline values were 35\% and 38\%, respectively.

The predicted values for continuous ADT are slightly higher than might be expected based on the Calais da Silva et al. data given the longer time horizon evaluated; however, there is evidence to suggest that the effects of ADT on sexual function begin in the initial 15 – 24 months of therapy. Data from a larger cohort of the Calais da Silva et al. trial suggest that rates of SDF at 12 months and 24 months were similar for patients receiving intermittent ADT.\textsuperscript{67} Similarly in the larger cohort, at 24 months 8\% of patients reported being sexually active compared to 10\% who reported being sexually active at 15 months in the smaller cohort. The values predicted by the model are in line with what has been reported in the literature.\textsuperscript{53,68}

### 4.4 Cardiovascular Disease

The model predicted that, of patients treated with continuous ADT, a mean proportion of 0.446 (44.6\%) would have CVD (including both incident cases as well as patients with comorbid CVD at model entry) based on a lifetime horizon. Keating et al. reported that of
men without prevalent CHD who received ADT, 25.3% developed CHD. The mean age of men in the analysis was 74.2 years and the median follow up was 4.55 years (range 0 days – 10 years). The predicted proportion of patients with incident CVD in the model was 34.1%. This is slightly higher than the data from Keating et al. however a longer time horizon is evaluated in the model. Using median survival to determine the rate of developing incident CHD from Keating et al. the annual rate of developing incident CHD would be approximately 0.064. This is similar to the rate associated with an incident rate of 34.1% and a median survival of 78.9 months (0.063 per year). As expected based on the hazard ratio of 1.32 for continuous versus intermittent ADT (i.e. 0.758 for intermittent versus continuous ADT) used in the model, the overall mean proportion of patients with incident CVD predicted for intermittent therapy is lower at 0.282 (28.2%). No published clinical data evaluating cardiovascular events in patients treated with intermittent ADT was identified for comparison.

4.5 Hip Fracture Incidence

The estimated mean number of hip fractures per patient in the present analysis was 0.093 for patients in the continuous ADT arm. Based on an estimated mean survival of 83.7 months (undiscounted), this is associated with an incidence rate of 0.013 per patient per year. Smith et al. reported hip fracture incidence rates of 1.26% per patient per year for patients receiving androgen deprivation therapy based on claims data from men with non-metastatic prostate cancer. Shahinian et al. reported that 4.06% of patients receiving ADT experienced a hip fracture 12 to 60 months after diagnosis of prostate cancer. While the total number of hip fractures was not reported, assuming each patient experienced only one hip fracture, the estimated annual incidence rate would be just over one percent. Ito et al. predicted an incidence rate of 1.150% per patient year in their cost effectiveness of fracture prevention in men receiving ADT for localized prostate cancer.

While this suggests that the model predictions are in line with what is seen in other studies for patients on continuous ADT, no data were available to compare estimated fracture rates in the intermittent ADT arm. The estimated mean number of 0.080 hip fractures per patient
based on a mean OS of 83.6 months (undiscounted) is associated with an incidence of approximately 0.011 per patient per year. This is slightly higher than incidence rates of 0.97% reported by Smith et al. for men who are not receiving ADT. Shahinian et al. reported that 2.06% of patients not receiving ADT experienced a hip fracture 12 to 60 months after diagnosis of prostate cancer, also suggesting an annual incidence rate of less than one percent. This suggests the predicted incidence of hip fracture in the intermittent arm is higher than reported rates for men not receiving ADT. This is what would be expected based on the model design and assumptions that bone loss is attenuated during the off-treatment phase of intermittent ADT, and similar to the rate of bone loss for those receiving ADT during the on-treatment phase.

4.6 Costs

The present analysis resulted in mean total estimated costs (undiscounted) of $141,900 for continuous ADT and $124,628 for intermittent ADT. In a study by Krahn et al. which evaluated costs (2004 CAD) associated with prostate cancer by phase of disease, the mean costs were reported to be $3,289/100 days in the first 12 months following diagnosis (Phase II), $1,495/100 days during the period of continuing care (Phase III), $5,629/100 days in the penultimate 12 months of life (Phase IV), and $16,020/100 days in the last 6 months of life (Phase V). Based on regression analyses, the costs per 100 days in each phase were higher for men with advanced disease relative to referent group. The referent group included patients with localized disease, aged 65–69 years, with a Charlson-Deyo score of 0, in the highest income quintile, residing in an urban area. The estimated cost/100 days in each phase for patients with advanced disease were $6,311, $1,945, $5,500, and $17,167 in Phase II, III, IV, and V, respectively. Given the model-estimated survival for patients with advanced disease of 83.7 months (undiscounted), the time in the continuing care phase is estimated to be 53.7 months (83.7 months less a total of 30 months in the three other phases) at a total cost of $38,040 (assuming each month is 30.4 days). The resulting total cost over the entire 83.7 month period equates to $112,439 ($128,222 in 2011 CAD). These results are slightly lower than the model predicted; however, the study by Krahn et al. did
not report costs by ADT status. Furthermore, age was also associated with higher costs, suggesting that the estimates from the present analysis are in line with what would be expected based on the cohort evaluated.

Bayoumi et al. reported lower estimates of total costs for men treated with combined ADT from a US perspective (1998 USD). The authors reported a total cost of $46,200 for patients treated with combined ADT with a non-steroidal anti-androgen plus an LHRH agonist. Based on the exchange rate at the time of 1.48 CAD to 1 USD, and adjusting for inflation, the total cost in 2011 dollars would be approximately $90,319. This is lower than predicted in the present analysis. This may be because estimates were taken from various published sources at the time and may not reflect differences in treatment patterns over time.
5 Results

5.1 Base Case Analysis

Results from the model for each treatment arm are summarized in Table 7. Intermittent therapy was associated with a gain of approximately 0.7 QALM (discounted) based on projected mean total QALMs (47.0 QALMs for intermittent ADT versus 46.3 QALMs for continuous ADT). The distributions of QALMs estimates for intermittent and continuous ADT from the analysis are presented in Figure 10 and Figure 11, respectively. The median quality-adjusted survival was estimated to be 45.9 (90% CI 25.6 – 65.7) QALMs for intermittent ADT versus 45.6 (90% CI 31.4 - 61.4) QALMs for continuous ADT. Intermittent ADT was also associated with lower costs compared to continuous ADT ($94,460 versus $109,431 for intermittent and continuous ADT, respectively). The distributions of cost estimates for each arm of the model are presented in Figure 12 and Figure 13.

Table 7. Base Case Results from Markov Monte Carlo Simulation

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Discounted Costs per Patient</th>
<th>Discounted QALMs per Patient</th>
<th>Discounted LMs per Patient</th>
<th>Undiscounted Costs per Patient</th>
<th>Undiscounted QALMs per Patient</th>
<th>Undiscounted LMs per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>$109,431</td>
<td>46.3</td>
<td>65.1</td>
<td>$141,900</td>
<td>58.5</td>
<td>83.7</td>
</tr>
<tr>
<td>SD</td>
<td>$133,795</td>
<td>11.8</td>
<td>18.4</td>
<td>$180,157</td>
<td>19.1</td>
<td>31.5</td>
</tr>
<tr>
<td>INT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>$94,460</td>
<td>47.0</td>
<td>64.7</td>
<td>$124,628</td>
<td>59.6</td>
<td>83.6</td>
</tr>
<tr>
<td>SD</td>
<td>$134,238</td>
<td>14.0</td>
<td>21.0</td>
<td>$183,830</td>
<td>22.5</td>
<td>35.8</td>
</tr>
<tr>
<td>Incremental (INT minus CONT)</td>
<td>-$14,971</td>
<td>0.7</td>
<td>-0.4</td>
<td>-$17,272</td>
<td>1.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

INT = intermittent; CONT = continuous; QALM = quality adjusted life months; LM = life months
Numbers not exact due to rounding
Figure 10. Distribution of Total QALMs for Intermittent ADT from Simulations

Figure 11. Distribution of Total QALMs for Continuous ADT from Simulations

QALM = Quality Adjusted Life Month. Discount rate applied was 5% per year.
Figure 12. Distribution of Total Costs for Intermittent ADT from Simulations

Costs presented in 2011 Canadian Dollars. Discount rate applied was 5% per year.

Figure 13. Distribution of Total Costs for Continuous ADT from Simulations

Costs presented in 2011 Canadian Dollars. Discount rate applied was 5% per year.
On average, intermittent ADT is expected to dominate continuous ADT due to a lower cost with a small incremental benefit measured in QALMs. In contrast, continuous ADT is associated with slightly higher unadjusted survival (65.1 LM versus 64.7 DT; values discounted). This equates to 0.4 LM less for patients treated with intermittent therapy at a lower cost (i.e. less effective and less costly), on average. The differences in both QALM and LM are small and likely of small clinical significance. The distributions of incremental costs and incremental QALMs are presented in Figure 14 and Figure 15, respectively.

In the majority of simulations (96.1%), incremental cost-effectiveness ratios for intermittent ADT compared to continuous ADT fall into the two lower quadrants of the cost-effectiveness plane. This suggests that intermittent ADT dominates continuous ADT (is less costly but more effective) or, is both less costly and less effective. A scatter plot of incremental cost-effectiveness ratios is presented in Figure 16 based on a willingness to pay threshold of $50,000/QALY divided by 12 months.

**Figure 14. Distribution of Incremental Costs for Intermittent versus Continuous ADT**

Costs presented in 2011 Canadian Dollars. Discount rate applied was 5% per year.
Figure 15. Distribution of Incremental QLAMs for Intermittent versus Continuous ADT

QALM = Quality adjusted life month. Discount rate applied was 5% per year.

Figure 16. Scatter Plot of Incremental Costs and QALMs (WTP $4,167/QALM)

WTP = Willingness to pay, QALM = Quality Adjusted Life Month. Quadrant I = More costly and more effective; Quadrant II = more costly and less effective; Quadrant III = less costly and less effective Quadrant IV = less costly and more effective.
Given that a significant portion of the simulations fell into Quadrant III (43.9% of simulations), a cost-effectiveness acceptability curve is not presented. This is because incremental cost-effectiveness ratios in Quadrant III are positive even though outcomes are worse (less QALMS) because costs are also lower. Based on a willingness to pay threshold of $4,167/QALM ($50,000/QALY), a total of 9.2% of the 43.9% of simulations that fell into Quadrant III resulted in an incremental cost effectiveness ratio of less than $4,167/QALM. A total of 2.8% of simulations resulted in incremental costs and benefits that were greater than zero (Quadrant I). Of these 1.8% were less than $4,167/QALY. Additionally, 52.2% of simulations fell into Quadrant IV (i.e. intermittent ADT is superior to continuous ADT with greater benefits and lower costs). Only 1.1% of simulations fell into Quadrant II in which case intermittent ADT would be an inferior choice (less effective but more costly).

An optimality graph, which reflects the proportion of simulations in which each comparator results in the greatest number of NHBs, is presented in Figure 17. Based on a willingness to pay threshold of $4,167/QALM, intermittent ADT was the optimal choice in 88.8% of the simulations. The distributions of NHBs and incremental NHBs for both intermittent and continuous ADT in the base case analysis are included in Appendix A.

The model predicted a lower mean number of hip fractures per patient for patients treated with intermittent ADT (0.080 per patient per year) compared to continuous ADT (0.093 per patient per year). Similarly the mean proportion of patients with CVD and SDF (incident plus prevalent cases) was lower for intermittent ADT. The model predicted that 28.2% of patients treated with intermittent ADT would develop incident CVD and 7.8% would develop incident SDF. In contrast, 34.1% and 22.3% of patients on continuous ADT would develop incident CVD and SDF, respectively. Table 8 summarizes adverse event results predicted by the model. The distributions for number of hip fractures, proportion of patients with CVD, and proportion of patients with SDF are included in Appendix B.
Figure 17. Proportion of Simulations Optimal by Treatment Strategy (WTP $4,167/QALM)

![Proportion Optimal by Treatment Strategy](image)

WTP = Willingness to pay, CONT = Continuous ADT, INT = intermittent ADT. The optimal treatment is the treatment which results in the greatest net health benefits based on the willingness to pay threshold.

Table 8. Summary of Adverse Event Results from Markov Monte Carlo Simulation

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Total Number of Hip Fractures per Patient</th>
<th>Proportion of Patients with CVD*</th>
<th>Proportion of patients with SDF*</th>
<th>Time without SDF (months)</th>
<th>Time on ADT Therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONT</td>
<td>Mean</td>
<td>0.093</td>
<td>0.446</td>
<td>0.870</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.038</td>
<td>0.099</td>
<td>0.067</td>
<td>5.5</td>
</tr>
<tr>
<td>INT</td>
<td>Mean</td>
<td>0.080</td>
<td>0.387</td>
<td>0.725</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.037</td>
<td>0.093</td>
<td>0.077</td>
<td>10.6</td>
</tr>
</tbody>
</table>

**INT** = intermittent; **CONT** = continuous; **QALM** = quality adjusted life months; **LM** = life months; **CVD** = cardiovascular disease; **SDF** = sexual dysfunction; **ADT** = androgen deprivation therapy.

* Total proportion includes incident and prevalent

5.2 Scenario Analyses

5.2.1 Only Patients with Metastatic Disease

Results from scenario analyses are summarized in Table 9. For patients with metastatic disease only, intermittent ADT was associated with an additional $8,818 in mean costs compared to continuous ADT. The difference in mean QALMs was an additional 4.6 QALMs for intermittent ADT (mean = 32.4 QALMS) versus continuous ADT (mean = 27.8 QALMs).
Patients with metastatic disease treated with intermittent ADT also had a longer mean life expectancy relative to continuous ADT. This is because the reported HR for OS for continuous versus intermittent ADT reported in the Calais da Silva et al. trial was higher than in the total population (HR for patients with metastatic disease = 1.26 versus 0.99 for total population). Therefore, the relative difference between continuous and intermittent ADT is larger in this scenario analysis. It should be noted that the data for patients with metastatic disease were from a smaller sample of patients in the Calais da Silva et al. trial (n = 191). The estimated mean incremental cost effectiveness ratio in patients with metastatic disease was $1,931/QALM. In patients with metastatic disease, intermittent ADT was the optimal choice in 86.4% of simulations as shown in Figure 18.
<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Discounted Costs per Patient</th>
<th>Discounted QALMs per Patient</th>
<th>Discounted LMs per Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 1: All patients metastatic at model entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONT</td>
<td>Mean $103,235</td>
<td>27.8</td>
<td>42.4</td>
</tr>
<tr>
<td></td>
<td>SD $225,141</td>
<td>8.8</td>
<td>14.7</td>
</tr>
<tr>
<td>INT</td>
<td>Mean $112,053</td>
<td>32.4</td>
<td>49.7</td>
</tr>
<tr>
<td></td>
<td>SD $283,493</td>
<td>10.2</td>
<td>17.2</td>
</tr>
<tr>
<td>Incremental (INT minus CONT)</td>
<td>Difference $8,818</td>
<td>4.6</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Scenario 2: No prevalent SDF in cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONT</td>
<td>Mean $114,791</td>
<td>46.7</td>
<td>64.4</td>
</tr>
<tr>
<td></td>
<td>SD $145,040</td>
<td>11.9</td>
<td>18.2</td>
</tr>
<tr>
<td>INT</td>
<td>Mean $99,239</td>
<td>47.6</td>
<td>63.6</td>
</tr>
<tr>
<td></td>
<td>SD $143,398</td>
<td>14.2</td>
<td>20.8</td>
</tr>
<tr>
<td>Incremental (INT minus CONT)</td>
<td>Difference -$15,552</td>
<td>0.9</td>
<td>-0.7</td>
</tr>
<tr>
<td><strong>Scenario 3: Younger men with no prevalent SDF and no prevalent CVD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONT</td>
<td>Mean $127,432</td>
<td>54.1</td>
<td>74.1</td>
</tr>
<tr>
<td></td>
<td>SD $166,425</td>
<td>15.5</td>
<td>23.2</td>
</tr>
<tr>
<td>INT</td>
<td>Mean $107,773</td>
<td>53.7</td>
<td>71.2</td>
</tr>
<tr>
<td></td>
<td>SD $160,478</td>
<td>17.7</td>
<td>27.1</td>
</tr>
<tr>
<td>Incremental (INT minus CONT)</td>
<td>Difference -$19,659</td>
<td>-0.3</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

INT = intermittent; CONT = continuous; QALM = quality adjusted life months; LM = life months; SD = Standard Deviation
Figure 18. Proportion of Simulations Optimal in Scenario Analysis of Patients with metastatic disease by Treatment Strategy (WTP $4,167/QALM)

CONT  INT

Option

Proportion Optimal

0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1

WTP = Willingness to pay, CONT = Continuous ADT, INT = intermittent ADT. The optimal treatment is the treatment which results in the greatest net health benefits based on the willingness to pay threshold.

5.2.2 No Prevalent Sexual Dysfunction at Model Entry

In a subpopulation of the base case cohort that included men with no pre-existing SDF, intermittent ADT resulted in 0.8 additional QALMs over continuous ADT. The mean proportion of patients with SDF was 0.222 for intermittent ADT compared to 0.627 for continuous ADT. Mean costs as well as LMs for intermittent and continuous ADT were similar to the base case results. Intermittent ADT dominated continuous ADT and was the optimal choice in 89.4% of the simulations due to the quality of life benefit (Figure 19).
5.2.3 Younger Men with No Prevalent Comorbidities at Model Entry

In younger men with no comorbid CVD or SDF intermittent ADT dominated continuous ADT with greater incremental QALMs than the base case analysis. In this patient population, intermittent ADT was associated with 0.3 fewer QALMs (discounted) and 2.7 fewer LM (discounted) compared to continuous ADT. Nonetheless, based on a willingness to pay threshold of $4,167/QALM, intermittent ADT was the optimal choice in 84.2% of simulations (Figure 20). Compared to the base case analysis, intermittent ADT was associated with fewer hip fractures (mean 0.065 hip fractures per patient vs 0.080 in the base case). The mean proportion of patients with SDF in the intermittent arm was 0.243 compared to 0.670 for continuous ADT. The proportion of patients with CVD in both arms was higher than in the base case. This is because of the longer follow-up time and the fact that rate of developing CVD was assumed to be the same in the base case analysis and not adjusted for age. Similar to the base case analysis, intermittent ADT was associated with a lower
proportion of patients with CVD compared to the continuous arm (mean proportion of patients with CVD 0.340 vs 0.423).

**Figure 20. Proportion of Simulations Optimal in Scenario Analysis of Younger Men without Sexual Dysfunction or Cardiovascular Disease at Baseline by Treatment Strategy (WTP $4,167/QALM)**

WTP = Willingness to pay, CONT = Continuous ADT, INT = intermittent ADT. The optimal treatment is the treatment which results in the greatest net health benefits based on the willingness to pay threshold.
6 Discussion

The present analysis suggests that intermittent therapy is a cost-effective option relative to continuous ADT based on a willingness to pay threshold of $50,000/QALY ($4,167/QALM). It should be noted that while there is no universally accepted willingness to pay threshold, $50,000/QALY is within suggested guidelines and is often cited in North America.99 Intermittent ADT was associated with a small mean quality-adjusted survival benefit compared to continuous ADT. Due to the expected benefits on BMD and SDF, survival adjusted by quality of life is expected to be higher, on average, in men treated with intermittent ADT. This is aligned with data suggesting that quality of life of patients treated with intermittent therapy is improved during the off-treatment phase.8,67,68 The differences were small and of uncertain clinical significance. In addition, intermittent ADT was associated with slightly shorter OS compared to continuous ADT, on average. Overall both quality-adjusted and unadjusted OS is anticipated to be similar for both treatment arms as would be expected based on results from previous studies comparing intermittent and continuous ADT.11,12,13,14 While there may be some tradeoffs in terms of cancer-specific survival associated with intermittent ADT; lower rates of death due to other causes, such as CVD, appear to offset any differences in OS for continuous ADT.11 Overall, the small difference in OS but slightly higher quality-adjusted survival suggests that, excluding cost considerations, the decision to use intermittent or continuous ADT is dependent on patient preferences. This is further demonstrated by the finding that the difference in costs and outcomes resulting from simulations were positive in some instances and negative in others.

The estimates of incremental cost/QALM calculated from simulations in the model fell into two main areas of the cost effectiveness plane: Quadrant II and Quadrant III. There is some ambiguity when interpreting the distribution of incremental cost-effectiveness ratios in a cost-effectiveness acceptability curve in a scenario where this is the case. This is because the incremental cost-effectiveness ratio is positive in Quadrant III as well as Quadrant I though the meaning differs.102 In Quadrant III of the cost-effectiveness plane, intermittent
ADT is both less costly and less effective resulting in an incremental cost per QALM that is positive. The probability distribution of the incremental cost per QALM is difficult to interpret because it does not provide this context. Due to the number of instances in which this occurred in the present analysis, a cost-effectiveness acceptability curve was not presented. Instead, results were presented based on incremental NHBs. Based on a willingness to pay threshold of $4,167/QALM ($50,000/QALY), intermittent ADT was the preferred option in 88.8% of simulations in the base case analysis when considering NHBs.

The present analysis suggests that intermittent ADT may be of more benefit in men with metastatic disease based on the findings of Calais da Silva et al.\textsuperscript{11} Using a willingness to pay threshold of $4,167/QALM ($50,000/QALY), intermittent ADT was found to be cost effective in this patient population with additional costs but greater effectiveness over continuous ADT. Unlike the base case analysis where the cost of intermittent ADT was less than continuous ADT, in the analysis of patients with metastatic disease, intermittent ADT was more costly on average. This is likely because the difference in OS between intermittent and continuous ADT was greater in this scenario than the base case analysis, which results in additional resource utilization. The incremental difference in QALMs between intermittent and continuous ADT was higher than in the base case analysis though by a smaller margin than OS. This may be due to the HRs for progression and OS that were used in the analysis. Patients overall may live longer. Because rates of progression are similar, the time spent in healthy states is comparable. The greater difference in incremental QALMs may therefore be due to longer survival.

In the scenario analysis of patients without comorbid SDF at model entry, the converse was true. Incremental QALMs between intermittent and continuous ADT were greater than in the base case analysis while the difference in incremental OS was slightly longer (-0.7 LMs in the scenario analysis versus -0.1 LMs in the base case analysis). Overall the mean time without SDF was higher in both arms compared to the base case analysis. In patients without prevalent SDF, quality of life at baseline was higher and since the rate of developing de novo SDF was lower for patients on intermittent ADT, there is a benefit in terms of
QALMs. That is, quality of life is higher in patients treated with intermittent ADT due to fewer cases of SDF and a higher quality of life for patients who do not experience SDF relative to the base case population.

In the analysis of younger patients without comorbidities, the incremental differences in QALM and LM for intermittent ADT versus continuous ADT were -0.3 and -2.7, respectively. One would expect that in a scenario analysis where there are no comorbidities, intermittent ADT should be associated with greater incremental QALMs compared to continuous ADT. However, the relative PFS for intermittent versus continuous ADT has an indirect impact on OS in the model because the probability of death after progression to hormone refractory disease is assumed to be the same in both treatment arms. The probability of progression in this scenario analysis was assumed to be the same as in the base case and progression to hormone-refractory disease is associated with a significantly higher probability of death compared to stable disease. As a result of patients being slightly younger at the start of the analysis, the probability of death from all causes is lower than in the base case analysis and patients are more likely to be at risk of progression. In the base case analysis, intermittent ADT was associated with a faster rate of progression based on the data from Calais da Silva et al.\textsuperscript{11} Therefore, in the scenario analysis, the differences in total LMs for continuous ADT compared to intermittent ADT are greater relative to the base case analysis which leads to greater mean total QALMs. The additional OS for continuous ADT outweighs the quality of life benefits associated with intermittent ADT. It should be noted that, the difference in incremental QALMs is much smaller than the difference in LM for continuous ADT compared to intermittent ADT. Furthermore, the difference in QALMs is small and intermittent ADT is associated with lower overall costs. As a result, intermittent ADT was the preferred option in more than 80% of simulations in this scenario analysis. This reinforces the finding that intermittent ADT is associated with better tolerability compared to continuous ADT. If the probability of progression was assumed to be lower for intermittent ADT compared to continuous ADT, as has been reported in various studies, the model would predict intermittent ADT was associated with greater QALMs compared to continuous ADT in a population of younger men without comorbidities.
In all scenarios analyzed, intermittent ADT was determined to be the optimal choice in the majority of simulations when considering quality-adjusted survival, though the differences in total QALMs were small. In most of the analyses performed, the difference in mean total LM between the two treatment options was also small. The exception may be the scenario which focused on patients with metastatic disease where intermittent ADT resulted in additional LMs, on average, compared to continuous ADT. Only one study was available that reported a HR for survival in this patient group and therefore there is significant uncertainty.

Several limitations must be considered when interpreting these results. In general, the lack of data from randomized controlled trials comparing intermittent to continuous ADT resulted in a number of assumptions that were used in the model. These assumptions are based on published data evaluating the relationship between ADT and adverse effects in prostate cancer of various stages. Therefore, there may be differences between outcomes in the present population that are not reflected. In general, the effects of ADT on adverse effects are assumed to be more directly related to the effects of therapy rather than disease stage. To date, no other models have been identified in the published literature that compared intermittent and continuous ADT. This overall data gap results in some difficulties validating the predicted values.

Costs included in the present analysis were mainly sourced from published and unpublished studies and therefore limitations associated with how the original data were collected and analyzed remain in the present evaluation. In addition, mean prostate cancer health state costs were based on data from a cohort of patients that may not be entirely representative of the population simulated in the model. There may also be some double counting if the costs collected for these patients included comorbid conditions. The overall impact of differences in health state costs on the results would not likely lead to a different conclusion. In addition, a key contributor to the difference in cost between intermittent and continuous ADT is likely associated with the cost of hormone therapy itself, given that patients in the intermittent arm are predicted to spend less time, on average, on ADT (mean
of 22.4 months compared to 56.8 months for continuous ADT). Therefore, differences in health state costs are not likely to impact the conclusions of this analysis. This could change if data are presented suggesting the incidence of hip fractures and CVD associated with intermittent ADT are significantly higher than continuous ADT, but this seems unlikely based on the current evidence and our understanding of the pathophysiology of the side effects of ADT.

The trials that were used in the analysis to provide parameter estimates related to survival and adverse events used various different forms of ADT. One of the limitations of this approach is that differences in survival and adverse event rates may not be the same for all ADT therapies. For example, the trial by Calais da Silva et al. which provided an estimate of cardiovascular risk between the two treatment groups was based on cyproterone therapy. The observed higher rates of cardiovascular deaths in the continuous arm may have been a result of the selected pharmacotherapy. Furthermore, using incident CVD rates from a study of prostate cancer patients with locoregional disease who did not receive ADT as a proxy for rates associated with intermittent ADT arm may have resulted in an underestimate of the true cardiovascular risk. Similarly, using hazard ratios for cardiovascular death in the continuous arm of the trial as a proxy for CVD may have resulted in an overestimate. The model used distributions to reflect this uncertainty and these included the possibility that the hazard ratio for CVD in the continuous arm relative to intermittent ADT was less than or equal to 1.0. In addition, some differences in the patient populations from the two studies must be considered. In the trial by Calais da Silva et al. the patients generally had more advanced disease than the cohort of patients reflected in the study of administrative data. No evidence was found to suggest that the adverse effects of ADT relate to the stage of cancer itself.

To ensure the model was robust and reflective of the disease, in addition to using probabilistic analyses for key input variables, several analyses were performed to validate the predictions of key adverse events against published clinical data. Where no clinical data were available for comparison, the model outcomes were compared to expected values.
based on the inputs as another validation step. In most cases, the predicted values in the continuous arm were consistent with what has been published in trials of combined ADT where treatment was given on a continuous basis. Values predicted in the intermittent arm were in line with what would be expected based on the relative effect on key outcomes.

The mean time on therapy was assumed to be 4 months for all cycles of intermittent ADT. In the first cycle, the on-treatment phase was followed by an off-treatment period of 15.4 months with a declining off treatment phase in subsequent cycles. In general, there appears to be less variability in the duration of the on-treatment phase compared to the off-treatment phase based on literature reviews. In clinical practice, the duration of each phase of a cycle of intermittent therapy is based on PSA levels and therefore the duration of the off therapy phase may be shorter or longer than what was used in this analysis. For example, different jurisdictions may use different PSA cutoffs when determining when to restart ADT. The duration of the off-treatment phase impacts estimates of costs (due to the high cost of hormone therapy) as well as estimates of quality of life in the model due to the utility decrement associated with ADT therapy.

The number of predicted fractures may also be affected by a shorter off-treatment phase because the model assumes that BMD decreases at a rate that is similar to men not receiving ADT when hormone therapy is stopped in the intermittent ADT arm. For men on continuous ADT, it was assumed that BMD continues to decline at the same rate over time, which may over or underestimate the fracture rates in the model. Results from the present analysis predict 0.093 and 0.080 hip fractures per patient on average for continuous and intermittent ADT, respectively. These are similar to what would be expected based on fracture rates for men who receive ADT from clinical studies as well as other cost-effectiveness models looking at the effects of ADT on BMD. Ito et al. evaluated the effects of fracture prevention on men receiving ADT. The model developed by the authors predicted an incidence rate of 1.15% hip fractures per patient per year for men receiving ADT. The predicted mean number of fractures in the intermittent arm of the present analysis was slightly higher than fracture rates for men with prostate cancer who did not
receive ADT as reported by Smith et al.\textsuperscript{50} This is what would be expected due to effects on BMD during the on treatment phase of each cycle. Shahinian et al. reported that fracture risk was higher as the number of doses of ADT administered increased.\textsuperscript{51} This suggests that intermittent therapy may be associated with a lower fracture risk than continuous ADT due to fewer doses. As more evidence is generated evaluating the number of fractures experienced by men on intermittent versus continuous ADT, a more robust analysis will be possible.

The present model uses background mortality, the relative risk of death associated with hip fractures and cardiovascular disease as well as prostate cancer-specific mortality to estimate OS. This approach could lead to an overestimation of mortality risk due to double counting. In addition, transition probabilities were determined based on the assumption that rates were constant and assumed survival followed an exponential curve. In the absence of raw data, no line of best fit could be established and the probability of death from hormone-refractory disease had to be estimated based on assumptions; therefore, survival could be over or underestimated. A validation process was used to ensure consistency with available data. The predicted survival curve in the continuous ADT arm of the model was in line with median OS estimates reported in the clinical trials as well as estimates from other cost-effectiveness analyses.\textsuperscript{11,72} Bayoumi et al. predicted an OS of 7.54 years (undiscounted) for CAB in patients with locally advanced disease.\textsuperscript{72} The present model predicts a mean survival of 7.0 years without discounting (83.7 months). One factor contributing to the difference in predicted survival is that the present analysis includes older patients. Estimates of quality-adjusted survival in the present analysis (46.3 QLAMs or 3.7 QALYs) were lower than those reported by Bayoumi et al. in their analysis (5.05 QALYs) for combined ADT.\textsuperscript{72} The discount rate in the present analysis was higher (5\% versus 3\%) and prostate cancer-specific health states considered differed somewhat from those included in the analysis by Bayoumi et al.\textsuperscript{72} The utility weights applied were also different.

A further limitation of the present analysis is that self-reported sexual activity was used as a proxy measure of SDF. The definition of SDF was not well-characterized in the trial. This may
have resulted in an over or underestimate of the probability of developing SDF in the model. The negative effects of ADT on sexual function are well known; however, the longer term effects of intermittent therapy on SDF are not known. The definition of SDF may also have an effect on estimates of quality of life both in terms of the rate of developing SDF as well as utility values. The base case analysis assumes only 35% of patients did not have SDF (and therefore have sexual function) at entry. The beneficial effects of an intermittent treatment strategy may be much greater within a subgroup of men who are all functional prior to initiating ADT. This was the case in the second scenario analysis, which assumed all patients were sexually active at the start of simulations. Rates of developing SDF in the model were taken from a study that included patients with prevalent SDF and did not adjust for the effect of age on sexual activity.\textsuperscript{11}

Other adverse effects associated with ADT were also not directly considered in the present analysis. Calais Da Silva et al. reported that men treated with continuous ADT experienced significantly higher rates of hot flushes (23% vs 7%), gynaecomastia (33% vs 10%) and headaches (12% vs 5%) compared to those on an intermittent schedule.\textsuperscript{67} The present model tries to account for these differences by using a utility decrement while patients are on ADT. This assumes that all men receiving ADT experience the same effects on quality of life, not just those individuals who experience these adverse effects. In addition, there is some evidence to suggest that men receiving ADT are at increased risk of developing diabetes.\textsuperscript{36} No information could be identified at the time of this analysis about differences in the risk of developing diabetes for men treated with intermittent versus continuous ADT; therefore it was not included in the present analysis.

Differences in the methods and populations used to collect the utilities that were included in this analysis could also impact the overall results. This is because the benefit of intermittent ADT in the model was based on quality of life as opposed to unadjusted survival. In the base case analysis, continuous ADT was associated with greater mean survival (though small). One of the challenges with using utilities reported in the literature is that these do not always represent the states being considered in the cost effectiveness
model. In addition, for patients in combined health states, such as prostate cancer health states with other comorbid conditions, utility scores are often not available. In the present analysis, a multiplicative approach was used to combine utilities in the majority of cases. This method could over or underestimate the utility value for patients. This was done to avoid the possibility of calculating negative values, which is possible when using utility decrements. Distributions were used to reflect uncertainty in utility estimates prior to applying multiplication factors.

Finally, most of the data used in this analysis was sourced from published literature. There are inherent limitations with using such data including the potential for publication bias.
7 Conclusion

Intermittent ADT appears to be cost effective compared to continuous ADT in men with advanced prostate cancer when considering both quantity and quality of life. For most patients, clinical outcomes are very similar between strategies. Intermittent ADT is associated with a marginally better tolerability profile and marginally worse prostate cancer related outcomes. Overall, when these effects are considered together, differences between the two treatment strategies were small, suggesting the decision is preference-based. Patient preferences for cancer control and avoiding complications associated with hormone therapy should be considered in making individual treatment decisions. At a system level, intermittent ADT could result in savings. Additional clinical research comparing intermittent to continuous ADT is required to confirm these findings, especially data comparing rates of adverse events and quality of life.
Appendix A. Net Health Benefit and Incremental Net Health Benefit Distributions from Base Case Analysis

Figure 21. Distribution of Average Net Health Benefits Continuous ADT (WTP $4,167/QALM)

WTP = Willingness to Pay, QALM = Quality Adjusted Life Month.

Figure 22. Distribution of Average Net Health Benefits Intermittent ADT (WTP $4,167/QALM)

WTP = Willingness to Pay, QALM = Quality Adjusted Life Month.
Figure 23. Distribution of Incremental Net Health Benefits Intermittent vs Continuous ADT (WTP $4,167/QALM)

Figure 24. Cumulative Distribution of Incremental Net Health Benefits Intermittent vs Continuous ADT (WTP $4,167/QALM)

WTP = Willingness to Pay, QALM = Quality Adjusted Life Month.
Appendix B. Distributions of Adverse Events from Simulations in the Base Case Analysis

Figure 25. Distribution for Number of Hip Fractures per Patient for Continuous ADT

![Continuous ADT Distribution](image)

Figure 26. Distribution for Number of Hip Fractures per Patient for Intermittent ADT

![Intermittent ADT Distribution](image)
Figure 27. Distribution for Proportion of Patients with Cardiovascular Disease for Continuous ADT*

*Proportions include incident and prevalent cases. CVD = Cardiovascular Disease.

Figure 28. Distribution for Proportion of Patients with Cardiovascular Disease for Intermittent ADT*

*Proportions include incident and prevalent cases. CVD = Cardiovascular Disease.
Figure 29. Distribution for Proportion of Patients with Sexual Dysfunction for Continuous ADT*

*Proportions include incident and prevalent cases. SDF = Sexual Dysfunction.

Figure 30. Distribution for Proportion of Patients with Sexual Dysfunction for Intermittent ADT*

*Proportions include incident and prevalent cases. SDF = Sexual Dysfunction.
References


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