2021

Cost-effectiveness of exercise medicine for prostate cancer

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This thesis is presented in fulfilment of the requirements for the degree of
Doctor of Philosophy

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2021

Declaration

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Abstract

Background

Androgen deprivation therapy (ADT) is associated with numerous adverse effects that impact on quality of life and contribute further to the cost burden of prostate cancer (PCa) via treatment and supportive care. Exercise medicine is effective in slowing PCa progression, reversing treatment adverse effects and improving quality of life and survival of patients, however, no economic analyses have been conducted to determine whether exercise is cost-effective in this population.

Objectives

Firstly, to examine the adverse effects of ADT for PCa and the evidence supporting the use of exercise medicine in their management. Secondly, to conduct the first economic evaluations of exercise medicine in the management of the adverse effects of ADT for PCa to strengthen the evidence base for the development of effective health policy around exercise and PCa survivorship.

Methods

A systematic review was conducted to determine the incidence of the adverse effects of ADT for PCa. A rapid review examined the role of exercise in managing these adverse effects. Three economic evaluations were then conducted to determine the cost-effectiveness of supervised exercise for men with PCa receiving ADT. Two trial-based cost-effectiveness analyses (CEAs) compared exercise training and usual care (a suggestion to exercise). The first involved a preliminary randomised controlled trial (RCT) of exercise for 20 men with metastatic PCa. A value of information (VOI) analysis was also conducted to examine the need for and value of a larger trial. The second CEA involved a RCT of exercise for men previously treated with radiation therapy and ADT. For the third economic evaluation, a decision analytic Markov model was constructed to evaluate the cost-effectiveness of an exercise intervention in preventing falls and fractures for men with localised or locally advanced PCa receiving ADT. All economic analyses were conducted from a healthcare payer perspective and the primary outcome measure was quality adjusted life years (QALYs) gained. Uncertainty in the results was explored using deterministic univariate and probabilistic sensitivity analysis where appropriate.

Results

The systematic review generated incidence evidence for nine adverse effect groups and 19 sub-groups, with statistically significant increased risks in 17 sub-groups. The

rapid review revealed that exercise was effective in improving body composition, physical function and fatigue, as well as mitigating the bone loss, sexual dysfunction and psychosocial effects associated with ADT. The first within-trial CEA of exercise for men with metastatic PCa resulted in an incremental cost-effectiveness ratio (ICER) of $133,509 and a 30% probability of being cost-effective after three months at a willingness-to-pay of AU$50,000. VOI analysis suggested further research is likely to be cost-effective to conduct. The second within-trial CEA of exercise for men who received radiation therapy and adjuvant ADT for localised PCa resulted in an ICER of $64,235 and a 41 per cent probability of cost-effectiveness after six months at a willingness-to-pay of AU$50,000. For the modelled cost-utility analysis, the exercise intervention dominated usual care (a suggestion to exercise), as it was less costly and more effective. Net monetary benefit (NMB) was $102,112 and probabilistic sensitivity analysis showed a 58% probability of cost-effectiveness at a willingness-to-pay of AU$50,000.

Conclusion

This research is the first to examine the cost-effectiveness of exercise for men with PCa receiving ADT. Supervised exercise is effective in managing many adverse effects of PCa treatment and cost saving in preventing falls and fractures. Future efforts need to focus on strengthening the evidence base in exercise for ADT adverse effect management. Uncertainty in economic evaluation can be reduced with more comprehensive cost and outcome data, longer follow up and larger sample sizes. This research has the potential to translate into changes in clinical practice, better informed policy decisions, cost savings for healthcare payers, and ultimately, better health and quality of life for PCa patients, survivors and their families.

Acknowledgements

This PhD journey would not have been possible without the support and guidance of so many.

I would like to begin by thanking my primary supervisor, Professor Rob Newton, who was there to support me throughout, with sage advice and encouragement, all delivered with his trademark good humour. Without his knowledge, guidance, support and generosity, this PhD would not have been possible. Many thanks also to Professor Daniel Galvão for his continued support throughout my PhD, his generosity and passion for his subject are something I won't forget. Professor Dennis Taaffe was also very supportive and generous with his time, always providing incisive critiques of my work, Such is the culture created by these wonderful academics at the Exercise Medicine Research Institute, that I always felt one of the team, even when physically located at a distance.

I am enormously grateful to my primary health economics supervisor, Associate Professor Haitham Tuffaha, from whom I have learned so much, not only about health economics but also about collegiality, professionalism and management. He is an inspiration, a brilliant mind and one of the loveliest people I have had the pleasure of knowing and working with. I am also eternally grateful to Professor Paul Scuffham for his support and for providing me the opportunity to join the Centre for Applied Health Economics where I have made wonderful friends. I am also appreciative of the funding received from the Centre of Research Excellence in Prostate Cancer Survivorship which allowed me to focus on completing my PhD. Thanks must also go to Professor Suzanne Chambers for her support in all my recent prostate cancer endeavours; she is indeed an inspiration.

To Andrew Searles, one of the nicest human beings on the planet, I owe a depth of gratitude for kick starting my foray into health economics all those years ago. His constant guidance, support, belief and friendship are something I will treasure always.

A very special thankyou to Penny Reeves, my supervisor when I didn't have a health economics supervisor, the most wonderful colleague and friend, without whom I would surely have foundered. Her quick wit and sharp mind were the sunshine and light that kept me going; the knowledge she so generously shared was the foundation that made everything else possible.

A big thankyou to all my colleagues at Hunter Medical Research Institute HRE: Rod, Simon, Alexis, Zoe, Shefi, Shanthi, Xenia for being part of my journey. I consider myself very fortunate to be part of such a fabulous team.

To my Mum and Dad, who have been waiting for this day longer than most parents, I would like to express my heartfelt thanks for always believing in me and encouraging me to follow my dreams and for supporting me whenever and however they could. To my brother, Jason and sister in law, Mel and my four adorable nieces, I am forever grateful for my escapes to Denmark. I will never forget those cups of tea delivered to my room in silence but with big smiles, by Hannah and Indiana, when they were told not to interrupt me.

To Kevin, without whom this would not have been possible. I am thankful for his unwavering support, his calm in the face of adversity and his patience while I removed myself from the world in pursuit of my PhD.

And lastly, to my two beautiful daughters, Madeleine and Ruby, who have lived every minute of this, I owe an enormous debt of gratitude and love for enduring my PhD absence. None of it would have been possible without their support and I look forward to making up lost time.

Table of Contents

List of Publications

Included in this thesis are papers co-authored with other researchers. The bibliographic details and status for these papers are summarised as follows:

Chapter 2
Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU. (2020) Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Supportive Care in Cancer 28: 2079-2093.

Chapter 3
Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU. (2020) The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review. Supportive Care in Cancer 28: 5661-5671.

Chapter 5
Edmunds K, Scuffham P, Reeves P, Galvão DA, Taaffe DR, Newton RU, Spry N, Joseph D, Tuffaha H. Demonstrating the value of early economic evaluation alongside clinical trials: exercise medicine for men with metastatic prostate cancer. European Journal of Cancer Care (under review).

Chapter 6
Edmunds K, Reeves P, Scuffham P, Galvão DA, Newton RU, Jones M, Spry N, Taaffe DR, Joseph D, Chambers SK, Tuffaha H. (2020) Cost-effectiveness analysis of supervised exercise training in men with prostate cancer previously treated with radiation therapy and androgen deprivation therapy. Applied Health Economics and Health Policy 18(5): 727-737.

Chapter 7
Edmunds K, Scuffham P, Newton RU, Galvão DA, Tuffaha, H. Exercise in preventing falls and fractures for men with prostate cancer receiving androgen deprivation therapy: a modelled cost-utility analysis. BMC Cancer (under review).

Statement of contribution of others

I designed, undertook the research or analysis and was the lead author on all articles in the List of Publications above. Evidence of peer review or current status of paper, copyright statement, where required, and statement of contribution for each of these chapters are provided in Appendix 6 Co-authored publications.

(Signed) (Date) 22 November, 2020
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Supervisor: Pro

List of Abbreviations

ADT	Androgen deprivation therapy
AEP	Accredited exercise physiologist
BMD	Bone mineral density
BMI	Body mass index
CADT	Continuous androgen deprivation therapy
CBA	Cost-benefit analysis
CEA	Cost-effective analysis
CEAC	Cost-effectiveness acceptability curve
CLT	Central limit theorem
CRPCa	Castrate resistant prostate cancer
CTCAE	Common terminology criteria for adverse events
CUA	Cost-utility analysis
CVD	Cardiovascular disease
EBRT	External beam radiotherapy
EVPI	Expected value of perfect information
GnRH	Gonadotrophin releasing hormone
GP	General practitioner
HRQoL	Health related quality of life
HSPCa	Hormone sensitive prostate cancer
ICER	Incremental cost effectiveness ratio
iNMB	Incremental net monetary benefit
IADL	Instrumental activities of daily living
IADT	Intermittent androgen deprivation therapy
LHRH	Luteinising hormone releasing hormone
LYs	Life years
MAUIs	Multi-attribute utility instrument
MBS	Medicare Benefits Schedule
NMB	Net monetary benefit
OOP	Out of pocket
PBS	Pharmaceutical Benefits Scheme
PCa	Prostate cancer
PSA	Prostate specific antigen
QALYs	Quality adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
RT	Radiotherapy
SRE	Skeletal related event
VOI	Value of information analysis

List of Tables

List of Figures

Chapter 1 General Introduction

Cancers are a major contributor to the burden of disease in Australia and have a considerable effect on the physical and emotional wellbeing of patients and their families. There is also a substantial social and economic impact, representing significant costs to the individual, family, community and the economy in terms of healthcare provision, absence from work, quality of life and premature mortality. Cancer accounts for about one-fifth (19%) of the total disease burden in Australia, making it the leading cause(1). An ageing population, lifestyle, environmental factors and diagnostic testing have resulted in an increasing number of cancer diagnoses in Australia in recent years. In 2020, it is estimated that almost 145,000 new cases of cancer will be diagnosed and there will be around 48,000 deaths from cancer(2). New developments in cancer therapy, a more personalised approach to medicine and new technologies contribute to the increasing costs of care. In addition, more people now survive a cancer diagnosis and require supportive care(3). In 2008-2009, according to the latest available data, cancer was responsible for $4.5 billion in allocated health expenditure, amounting to 4% of all government health expenditure(4).

1.1 Prostate cancer

Prostate cancer (PCa) is an increasingly significant public health issue. It is a heterogeneous disease with a high incidence and the cause of significant morbidity and mortality. In Australian men, it is the most commonly diagnosed cancer and the second most common cause of cancer death after lung cancer(2). In 2020, it is estimated 16,741 new cases of cancer will be diagnosed; in age-standardised rates, that is an estimated incidence of 110 cases per 100,000 males(2). Australia and New Zealand have the highest incidence rate in the GLOBOCAN database, which includes estimates of the incidence, mortality and prevalence for 36 types of cancer and for all cancers combined in 185 countries in the world(5). An estimated 3,152 Australian males are expected to die from PCa in 2020, corresponding to an age-standardised mortality rate of 21 deaths per 100,000 males(2).

PCa is an age-related disease and the incidence rate is expected to increase with age, peaking between 70 and 74 years of age, before decreasing with age. In 2020, there were an estimated 3498 cases of prostate cancer diagnosed in the 70-74 year age group(2). To age 75, the risk of PCa is one in seven men and by age 85, the risk increases to one in six, however less than 10% of men die from PCa(2). In 2020, the 5-

year survival rate was estimated to be 95%(2). Stage of PCa is a major contributor to survival. Men with local (organ confined) or regional disease (in the region of the prostate) have a 5-year survival rate of almost 100%, whereas men with distant metastatic disease have a 5-year survival rate of 36%(2). In Australia, over 80% of men are diagnosed with Stage I or II PCa(2). With the advent of increased testing, incidence of local and regional disease is increasing and metastatic disease is decreasing(6). The staging of PCa, the grading system used to determine prognosis, and ultimately inform the treatment pathway, are explicated below (Tables 3, 4 & 5).

The specific causes of PCa remain unknown; the only established risk factors are age, race or ethnicity and family history(7). The prostate is known to undergo structural changes as a result of diet, and hormonal changes that take place with ageing, which leads to alterations in genetic expression(7). While diet and lifestyle cannot be conclusively associated with an increased risk of prostate cancer, smoking does increase risk of mortality due to PCa, and obesity is associated with cases of higher grade and fatal disease(6). Insulin growth factor-1 (IGF-1), which is responsible for promoting cell proliferation and inhibiting programmed cell death, has been associated with PCa progression which provides a potential link with westernised diet, obesity and metabolic factors like insulin resistance(8). However, it is androgens and the androgen receptor that play a fundamental role in the development and progression of PCa(9).

1.11 Androgen deprivation therapy

In 1941, Huggins and Hodges(10) demonstrated that androgens fuel cancer growth and that androgen suppression, in the form of surgical (bilateral orchiectomy) or medical castration (oestrogen treatment), resulted in prostate cancer regression. This discovery heralded the beginning of hormone therapy as a treatment for advanced PCa. Two retrospective studies in the late 1940’s and early 1950’s concluded that patients treated with hormonal therapy (either oestrogens or orchiectomy) enjoyed a survival and quality-of-life advantage over patients in the pre-hormonal therapy era(11, 12).

While surgical castration is not associated with the same increases in myocardial infarction, coronary heart disease and cardiac death as some medications, it has largely been replaced by medical castration for reasons including reversibility, ease of administration, and cosmetic and psychological concerns(13, 14). Medical castration was initially carried out using oestrogen. However, oestrogens were associated with significant adverse effects such as thromboembolic and cardiovascular risk, as well as

feminisation(13-15). Since the development of luteinizing hormone-releasing hormones (LHRH) agonists and antagonists in the 1980's, oestrogen therapy fell largely out of favour. Since that time, medical means of androgen deprivation therapy (ADT) other than oestrogen have been the standard first-line therapy for metastatic prostate cancer. ADT has also been shown to have survival benefits for men with locally advanced or high-risk localised disease. Its use, however, has increased across the spectrum of disease(16). The use of ADT to treat many stages and grades of tumour among men of all ages has the potential to generate considerable costs to the individual, healthcare providers, and society. The types of ADT currently available in Australia and their modes of action are shown in Table 1 below.

Table 1 Androgen deprivation medications currently used in Australia

Type	Technical name	What it does	Format
GnRH/LHRH agonist	goserelin leuprorelin triptorelin	Inhibits GnRH release from the testes with continuous delivery to suppress testosterone production	injection
GnRH/LHRH antagonist	degarelix	Inhibits GnRH release from the testes by binding to pituitary GnRH receptors decreasing circulating levels of testosterone	injection
Androgen receptor blockers (anti-androgens)			
Steroidal	cyproterone acetate	Inhibits androgen receptor (AR) & central nervous system effects	tablet
Non-steroidal -1st generation	bicalutamide flutamide nilutamide	Inhibits AR, thereby reducing the stimulation of PCa cells	tablet
Non-steroidal - 2nd generation	enzalutamide apalutamide	Blocks several steps in the AR signalling pathway: binding to the AR; nuclear translocation of activates receptor; and association of the translocated receptor with DNA	tablet
Adrenal androgen inhibitors	abiraterone acetate + prednisone/ methylprednisolone	Inhibits androgen production at all sources: adrenal glands, testes, tumour	tablet

Abbreviations: GnRH gonadotrophin releasing hormones; LHRH luteinizing hormone-releasing hormones

Use of ADT is associated with significant adverse effects. These are numerous and can be particularly debilitating, even life threatening, so are a fundamental consideration in choice of treatment modality(14). As shown in Table 2, the range of adverse effects is broad and can be categorised into nine different groups according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5(17). A detailed discussion of the adverse effects associated with ADT, including their incidence/risk is presented in Chapter 2.

Table 2 Adverse effects of androgen deprivation therapy

Adverse effect group (CTCAE)		Sub-group
1	Musculoskeletal changes	Bone loss, osteoporosis, fracture
2	Metabolic changes	Body composition changes (increased fat mass, decreased muscle mass and strength), metabolic syndrome, diabetes
3	Cardiac disorders	Cardiovascular events (myocardial infarction, cardiac arrest, cardiovascular mortality)
4	Nervous system disorders	Cognitive impairment, stroke, dementia
5	Vascular disorders	Hypertension, thromboembolic events, hot flashes
6	Hepatobiliary disorders	Hepatic disorders
7	Reproductive system disorders	Gynaecomastia, breast pain, sexual dysfunction
8	Psychiatric disorders	Depression
9	General disorders	Fatigue, Gait disturbance

Abbreviations: CTCAE Common terminology criteria for adverse events

Adverse effects and their treatment are an important consideration in terms of the economic impact of ADT for PCa. For example, Lee et al.(18) found significant utility decrements for patients experiencing adverse events (fracture, musculoskeletal event, joint related symptoms, serious cardiovascular events) across all algorithms mapped to four health related quality of life questionnaires. The following section is an examination of the treatment of PCa and highlights the importance of ADT within treatment algorithms.

1.2 Prostate cancer treatment

Current treatment guidelines for PCa take a number of factors into consideration(16). A key determinant of primary treatment is estimated life expectancy which uses age and current quartile of health. Risk assessment involves consideration of serum PSA level, biopsy result, clinical tumour stage (size of tumour and how far it has spread) and Gleason score (abnormality of cancer tissue). The Gleason score is used to assign a histologic Grade group from 1 – 5 to express the aggressiveness of the cancer (Table 3) and the Tumour-Node-Metastasis staging system is used to determine the stage of the cancer (Table 4) (16, 19). How these systems are combined to determine prognostic groups and treatment is shown in Table 5. Other factors that impact on the risk of PCa and inform treatment decision making are family and personal history, as well as patient preferences(16).

Table 3 Prostate cancer grade groups

Grade group	Gleason score[1]	Gleason pattern[2]
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Notes: [1]Gleason score is the grading system used to score PCa aggressiveness (healthy cells-lower; unhealthy cells-higher). [2]Gleason pattern refers to a composite score comprising the primary grade (cells that make up the largest area) and the secondary grade (cells that make up the next largest area).

Table 4 Prostate cancer staging system

Prostate cancer stage	Definition
Clinical tumour (cT) descriptors	
T	Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is not palpable
T1a	Tumour in 5% or less of biopsy tissue
T1b	Tumour in more than 5% of biopsy tissue
T1c	Tumour identified by needle biopsy found in one or both sides, not palpable
T2	Tumour is palpable and confined within prostate
T2a	Tumour involves one-half of one side or less
T2b	Tumour involves more than one-half of one side but not both sides
T2c	Tumour involves both sides
T3	Extra prostatic tumour that is not fixed or does not invade adjacent structures
T3a	Extra-prostatic extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Lymph Node descriptors	
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)
Metastases descriptors	
M	Distant metastases
M0	No distant metastases
M1	Distant metastases
M1a	Non-regional lymph nodes
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Table 5 Prostate cancer prognostic groups

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA <20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Abbreviations: PSA prostate specific antigen; ng/mL nanograms per milliliter; cT clinical tumour; pT pathological tumour
Notes: see Table 4 for tumour (T), lymph node (N), Metastases (M) descriptors

1.2.1 Treatment options

In order to address the potential for overtreatment of PCa, it is recommended that men with a life expectancy of five years or less with very low, low or intermediate risk disease and no symptoms receive no workup or treatment until symptoms develop. Those with high or very high-risk PCa should undergo bone imaging and, if regional or metastatic disease is found, receive ADT. Observation is also an option if the risks and complications associated with treatment are considered greater than the benefits in terms of prolonged life or improved quality of life. Where there is no nodal involvement or metastases but high risk, external beam radiotherapy (EBRT) may be recommended (16).

For men with life expectancy of five years or more, treatment determination is based on assessment of risk guided by the prognostic groupings in Table 5. However, PCa is a complex disease with much controversy surrounding its management. A number of different primary treatment modalities are used for PCa such as observation, active surveillance, EBRT, radical prostatectomy or brachytherapy and ADT. Low risk, early stage disease tends to be treated with curative therapies such as prostatectomy, EBRT or brachytherapy, whereas ADT (LHRH agonist or orchiectomy) tends to be used for more unfavourable or high-risk disease, where there is regional or lymph node involvement (N1) or high risk of metastasis (M0). Androgen deprivation (LHRH agonist or LHRH agonist + antiandrogen) may also be used as a neoadjuvant, concurrent and/or adjuvant therapy with radiation therapy in such cases, with or without

abiraterone and prednisone or methylprednisolone. If the tumour is metastatic, orchiectomy or ADT of varied forms (i. LHRH agonist; ii. LHRH agonist + antiandrogen; iii. LHRH antagonist or iv. - i. or iii. + abiraterone with prednisone or methylprednisolone) are the treatments of choice (sometimes with the addition of chemotherapy-docetaxel)(16).

Once the tumour becomes resistant to the initial ADT, referred to as castrate resistant prostate cancer (CRPCa), ADT should be maintained to keep testosterone levels low and additional therapies applied. For non-metastatic CRPCa, additional therapies include addition of or switching to a different antiandrogen, (flutamide, bicalutamide, nilutamide, enzalutamide or apalutamide). For metastatic CRPCa, additional therapies include a different antiandrogen (as above, with the exception of apalutamide), an adrenal androgen inhibitor (abiraterone acetate + prednisone or methylprednisolone), docetaxel, palliative radiation therapy for bone metastases, immunotherapy (sipuleucel-T). Visceral metastases (liver, lung, adrenal, peritoneal, and brain) can be treated with the addition of all of the above (with the exception of sipuleucel-T), as well as chemotherapy (mitoxantrone + prednisone). With progression, subsequent therapy depends on prior therapy (whether docetaxel, enzalutamide or abiraterone + prednisone or methylprednisolone), but includes various forms of chemotherapy, secondary hormone therapy or immunotherapy (pembrolizumab)(16). It is evident from the above treatment guidelines that ADT is used broadly across the PCa disease spectrum, with the exception, in most circumstances, of lower risk, localised cancer.

1.3 Economic impact of ADT medications

The economic impact of ADT in Australia is significant. Based on Medicare services listed in the Medicare Benefits Schedule (MBS) and medicines listed on the Pharmaceutical Benefits Scheme (PBS), government expenditure for PCa treatment in 2012 (from initial appointment prior to diagnosis to 12 months post diagnosis) was highest for men receiving ADT ($16,883 per person) compared to other treatments such as EBRT ($13,310), orchiectomy ($13,282) and radical prostatectomy (RP) ($7,653)(AUD 2012)(20). Mean out-of-pocket (OOP) costs (AUD 2012) were also highest for men receiving ADT ($11,471) compared to watchful waiting ($5,492), active surveillance ($10,302) and RP ($10,996)(21). The broader application of ADT over time has resulted in a marked increase in the number of men receiving ADT for PCa in Australia. One study estimated an increase from 16,000 patients in 2003-2004 to

23,500 in 2008-2009(22, 23). Allan et al.(24) reported a steady increase of over 300% from 6,500 men using ADT in 1999-2000 to 21,800 in 2009-2010.

A number of ADT medications are currently available in Australia, however, GnRH agonists are most commonly used (Table 1)(25, 26). Medicare Australia(27), through the PBS, records the use and cost of ADT medications. The volume and cost of many ADT medications are still high and increasing, despite the reductions in cost associated with medications transitioning out of patent and being produced as multi-branded/generic pharmaceuticals(28). Cost figures are thus conservative indications of the real cost. For example, the cost of some generic medications fall below the co-payment, so do not register in any PBS cost or volume data(29).

Trends in PBS expenditure show that while prescriptions for generic medicines are becoming more popular than in the past, contributing to over 60% of prescription volumes in 2010/11, single patented medications account for 60% of government expenditure for the same period(29). This trend can be explained by some medicines coming out of patent, adding to volumes but not much to expenditure, while new, patented and costly medicines are also being released. This trend is demonstrated in Figure 1, where more recently released and costly single patented ADT drugs, like abiraterone acetate and degarelix, are rising more markedly in use, in contrast to generic drugs like leuprorelin and goserelin. It is these changes in practices that are also contributing to the rising cost of ADT medication.

It is important to note from Figure 1 that these estimates of ADT cost do not include the cost of the GP consult, patient co-payments or the cost associated with script dispensing. Nor do they include the cost of associated clinical treatments such as prostatectomy, radiotherapy or chemotherapy or the costs of supportive care. Some of these treatments could also have been provided in public hospitals and therefore not appear as MBS and PBS costs. In addition, not all ADT related costs could be included. One form of goserelin is used to treat breast cancer and endometriosis as well as PCa, so this cost was not included. Similarly, in the case of abiraterone acetate, which must be administered with a corticosteroid, it was not possible to distinguish administration of the corticosteroid for PCa purposes from other purposes, so this cost was also excluded. Over the period 2010 – 2018 (results January 2010 to November 30, 2018), the cost of ADT to the PBS has been $1.5 billion(30). This cost has increased each year and in 2018 the cost of ADT stood at $247 million(30). Goserelin, the most commonly used drug for the 2010-2018 period accounted for 34% of total costs ($492 million), followed by leuprorelin at 22% of total costs ($318 million),

enzalutamide at 20% of total costs ($285 million) after less than 5 years on the PBS, and abiraterone acetate at 16% of total costs ($227 million) after less than 6 years on the PBS. Other ADT drugs, comprising triptorelin, bicalutamide, flutamide, nilutamide and degarelix together had a 10% share of total costs ($76 million)(30). With the advent of new generation drugs like abiraterone acetate in 2013 and enzalutamide in 2014, costs for ADT have escalated, increasing over 1.5 times between 2013 and 2014 and by almost 2.5 times between 2013 and 2018. The share of total cost has also changed over the last five years. Enzalutamide holds a 27% share equal to goserelin, abiraterone acetate a 21% share and leuprorelin,18%. While the cost of ADT medications is significant, one cost that is often not considered is that of the adverse effects associated with treatment. ADT adverse effects and their consequent treatment, as well as the supportive care often needed, have the potential to add further costs to the considerable expense of ADT medication in the treatment of PCa. How much extra cost depends on how prevalent and how debilitating the adverse effects are, in addition to the cost of treating or managing them.

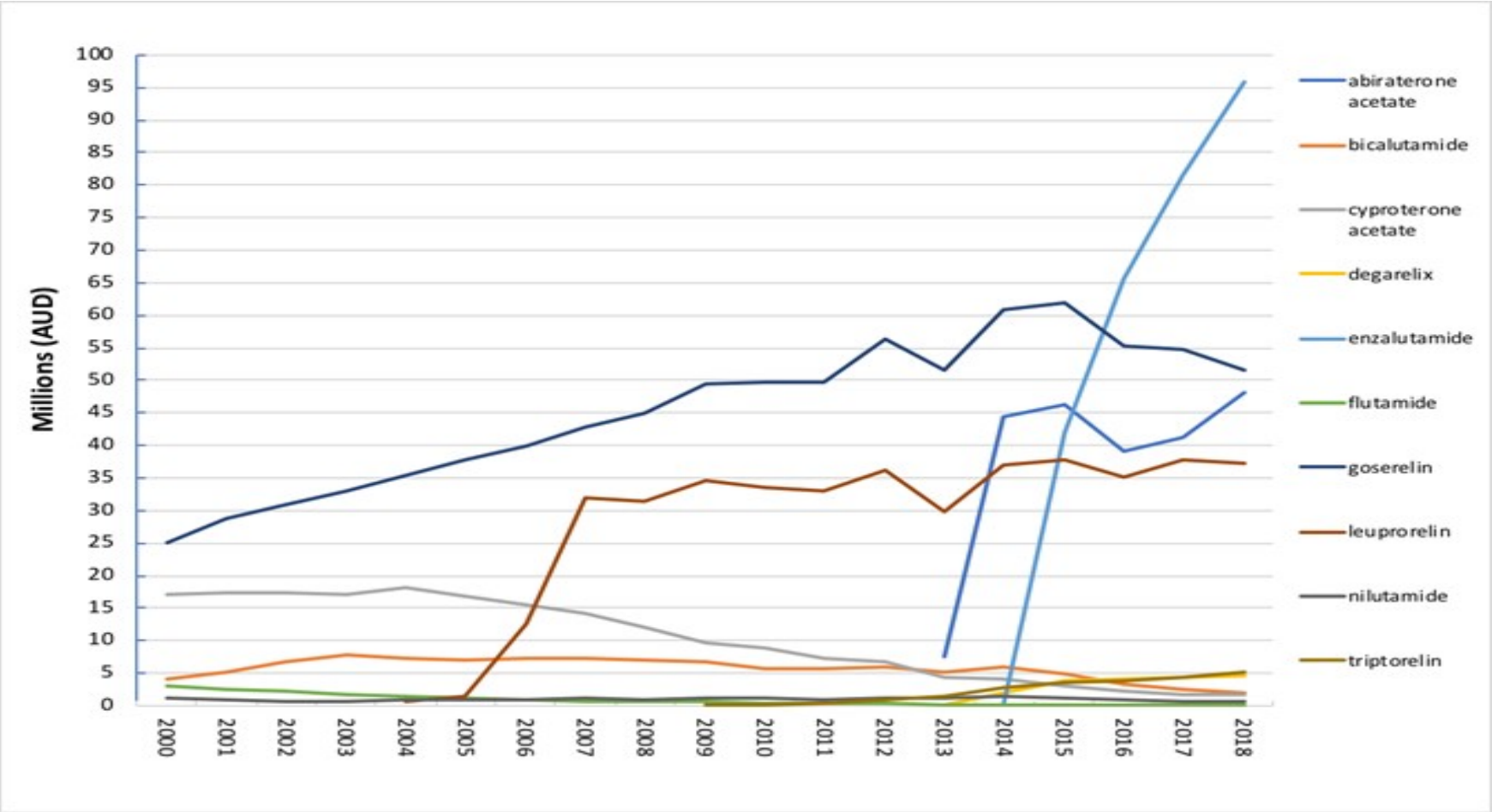


Figure 1 Cost of androgen deprivation therapy Australia 2000-2018 PBS (30)

ADT, in one form or another, is the only treatment used across the spectrum of PCa disease and therefore has the potential to generate considerable costs to the individual and society. The incidence of PCa increases with age, so with the demographic transition towards an ageing population and a greater uptake of PSA testing, the burden and cost of PCa is only likely to increase(31). This emphasises the importance of finding a cost-effective way of managing the adverse effects of ADT for PCa.

1.4 Exercise and the management of the side effects of ADT

It has been extensively demonstrated that physical exercise is an effective therapy that slows PCa progression, reverses treatment adverse effects and improves the wellbeing and quality of life of cancer patients(32-37). An early review of exercise interventions for cancer patients revealed evidence of benefits such as reduced fatigue, improved muscle function and physical performance, increased aerobic capacity, improved body composition and quality of life(38). Researchers focusing on PCa noted the impact of ADT adverse effects, reporting clinically significant decreases in lean muscle mass and strength as well as impaired physical functioning. Patients receiving ADT also had lower bone mineral density and increased fat mass compared to controls(39, 40). Research identifying further ADT adverse effects such as metabolic syndrome, heightened risk of diabetes and cardiovascular disease (CVD), prompted exercise physiologists to research the impact of exercise on preventing or reversing these adverse effects(41). Resistance exercise improved muscle strength, functional performance and balance, as well as maintaining body composition and reducing ADT adverse effects such as fatigue and levels of C-reactive protein(42). In addition, high intensity exercise was found not to impact on ADT efficacy(43). Further studies showed that exercise was beneficial for patients receiving both short term and long term ADT(44). As some of the adverse effects of ADT required a longer exercise intervention to demonstrate any benefits (bone loss, diabetes and CVD risk), a comprehensive randomized controlled trial (RCT) was conducted to determine the impact of exercise over 12 months(45). A significant finding from this RCT was that different modes of exercise address different aspects of ADT toxicity(46).

This growing body of evidence led to the publication, in 2009, of the Australian position statement on exercise and cancer that participating in exercise during and after cancer treatment is associated with benefits such as improvements in physical and psychosocial outcomes, reduced impact of disease symptoms and treatment

related side effects and better survival. The exercise prescription was moderate intensity exercise for at least 20 minutes 3-5 times per week, involving aerobic, resistance or mixed exercise(47). In 2010, a roundtable of experts was convened by the American College of Sports Medicine to develop exercise guidelines for cancer survivors(48). Their review of RCTs concluded that exercise for PCa survivors was safe, reduced fatigue and improved aerobic fitness, body composition, muscle strength, physical function and quality of life. The guidelines recommended that PCa survivors should aim to achieve a minimum of 150 minutes of moderate aerobic exercise a week, including at least two sessions of resistance exercises.

It wasn't until 2011, however, that a health professionals follow-up study examined physical activity and survival after PCa diagnosis(37). This study demonstrated a 49% lower risk of all-cause mortality and a 61% lower risk of PCa death in a sample of 2,705 men diagnosed with non-metastatic disease. A recent systematic review of the literature around the effects of exercise on the treatment related effects of ADT for PCa demonstrated improvements in lean body mass, muscular strength, physical function, cardiorespiratory fitness and fatigue with varied effects for adiposity(49). Exercise has thus been shown to be critical to health and quality of life, as well as survival, for PCa survivors.

In 2019, the Exercise and Sports Science Australia (ESSA) position statement and the American College of Sports Medicine (ACSM) guidelines were updated with current scientific evidence, clinical experience and exercise science principles. They emphasise the importance of an appropriate exercise prescription for cancer patients, which is individualised and targeted for the specific health issues most impacting the patient (50, 51). The ACSM guidelines for cancer survivors recommend moderate intensity aerobic training at least three times per week, for at least 30 minutes. The addition of resistance exercise to aerobic training, at least twice a week, using at least two sets of eight to 15 repetitions, results in similar benefits, though evidence suggests resistance training alone may not be enough (51). The ESSA guidelines recommend a more tailored approach with exercise mode and dosage prescribed specifically to ameliorate, in priority order, the health issues and mortality risks of greatest concern for the patient. Both these documents were based on extensive research reviews to ascertain the strength of evidence supporting the use of exercise for cancer patients and survivors. Strong evidence was available for a number of cancer-related outcomes: anxiety and depression, fatigue, health related quality of life (HRQoL) and physical function. Moderate evidence was also available for bone health and sleep.

While organisations such as the American Society of Clinical Oncology (ASCO) (52), the National Comprehensive Cancer Network (53) and the National Institute for Care and Excellence(54) have PCa survivorship guidelines that support exercise for adverse effect management, few cancer patients are able to meet these guidelines due to reasons of access to the level of care required, time constraints, physical, psychological and financial capacity, as well as concerns regarding the risk of inappropriate and potentially detrimental types and doses of exercise(55). More targeted and tailored guidelines alongside implementation strategies and policy support are needed to contribute to increased uptake of these evidence based guidelines(55).

Aside from the effectiveness of exercise in PCa adverse effect management, exercise is emerging not only as a targeted medicine delaying progression, reducing the risk of recurrence or improving survival(51, 56), but also as a synergistic medicine, increasing the effectiveness of other concomitant therapies such as chemotherapy or radiation therapy(56). While considerable evidence exists to support the use of exercise as an essential part of a cancer treatment and care plan, there has been limited uptake of this approach(57). Exercise has the potential to generate significant cost savings as well as improve quality of life for this population. It is expected that the use of exercise in cancer management may translate into health and economic benefits in improved quality of life and fewer complications, resulting in savings to the health care system through potential reductions in adverse effects and chronic diseases, enhanced productivity and reduced patient and carer burden.

1.5 Purpose

ADT is the standard first-line therapy for metastatic prostate cancer but also improves survival in men with non-metastatic, locally advanced or high-risk localised prostate cancer. It thus represents a significant cost in the treatment of PCa. In addition, ADT is associated with debilitating adverse effects with the potential to generate further costs from their subsequent treatment. Some adverse effects contribute to the development of chronic disease and long-term health utilisation and reduced quality of life. There is, therefore, a need for management strategies that minimise the burden of PCa treatment. A growing body of research has shown that exercise is effective at reducing and even preventing the adverse effects of ADT for PC survivors. Exercise also has the potential to manage the side effects of ADT in a cost-effective manner. To date, there has been no attempt to quantify the economic impact of exercise programs on PCa survivors, the healthcare system and society. The

purpose of this doctoral research, therefore, is to determine the economic impact of exercise in managing the adverse effects of ADT.

A comprehensive economic analysis of the role of exercise in the management of PCa would be invaluable in guiding effective policy and investment in health services. Given the broad application of ADT, across the disease spectrum, the economic analyses conducted in this thesis will include different stages of PCa. A systematic literature review will first set the scene for the research objective by evaluating the evidence on the adverse effects associated with ADT and their risk or incidence.

Two retrospective cost-effective analyses (CEAs) will be conducted alongside randomised controlled trials (RCTs) of exercise in the management of ADT adverse effects for two different populations(34, 36). Given the limitations associated with economic analyses of clinical trials such as lack of data (costs, outcome data applicable to economic analysis, missing data), small sample size and relatively short follow up, a modelled analysis will be conducted of the costs and consequences of exercise for the management of physical function decrements arising from ADT toxicity in the form of reduced muscle strength and increased bone loss. This modelled analysis will incorporate evidence from the literature, outcomes from clinical trials and expert knowledge to determine the cost-effectiveness of exercise in reducing falls and fractures for men with PCa receiving ADT. Discussion of the findings of this doctoral research, its implications, limitations and future directions, are provided in the final chapter.

1.6 Research questions

The research questions addressed in this doctoral research are:

1. What is the risk or incidence of the most common adverse effects of ADT for PCa patients? (Chapter 2)
2. What is the role of exercise in managing these adverse effects? (Chapter 3)
3. What is the cost-effectiveness of exercise in managing the adverse effects of PCa?
    - CEA 1: What is the cost-effectiveness of exercise in the management of advanced PCa or bone metastatic disease? (Chapter 5)
    - CEA 2: What is the cost-effectiveness of exercise in counteracting the long-term adverse effects associated with ADT for localised/locally advanced PCa? (Chapter 6)

- CEA 3: What is the cost effectiveness of exercise in reducing falls and fractures for men with PCa receiving ADT: a modelled cost-utility analysis? (Chapter 7)

4. What are the implications of exercise in the management of adverse effects of ADT for PCa? (Chapter 8)

1.7 Significance of the study

Australia's expenditure on health is growing at a faster rate than national income, therefore policy makers need to know what works, at what cost and how society will benefit from the investment. This doctoral research is significant in its potential to inform how exercise can reduce the significant burden of PCa in relation to its expense and contribution to reducing premature morbidity and mortality. While the effectiveness of exercise in reversing or even preventing many adverse effects of ADT for PCa is widely recognised, to date, no economic analyses have been conducted to demonstrate the impact of exercise on health and economic outcomes. The findings from this doctoral research will contribute to knowledge and strengthen the evidence base for the development of effective health policy. The outcomes of this research could mean changes to clinical practice, improved economic analysis of exercise interventions, better health and quality of life for PCa patients, survivors and their families, as well as cost savings or better return on investment for funding bodies.

Chapter 2 Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review

2.1 Introduction

Since the advent of PSA testing in the 1990s, the rising incidence and burden of prostate cancer (PCa) has been a cause for concern. Treatment options for men with PCa are varied and depend on a number of factors such as expected survival, risk of progression, stage and grade of cancer at diagnosis, age and health of the patient, family history, personal preferences of the patient and adverse effects of treatment. Androgen deprivation therapy (ADT) suppresses the production of androgen, which fuels the growth of PCa. It has broad application in the treatment of PCa and many types of ADT are currently in use in Australia (Table 6). ADT is predominantly used for intermediate or higher risk disease as well as advanced and metastatic cancer. It is also maintained when cancer becomes castration resistant. In addition, it is used as neo-adjuvant, concurrent and adjuvant therapy with prostatectomy and radiotherapy(16, 58-60).

Table 6 Androgen deprivation medications currently used in Australia

Type	Technical name	What it does	Format
GnRH/LHRH agonist	goserelin leuprorelin triptorelin	Inhibits GnRH release from the testes with continuous delivery to suppress testosterone production	injection
GnRH/LHRH antagonist	degarelix	Inhibits GnRH release from the testes by binding to pituitary GnRH receptors decreasing circulating levels of testosterone	injection
Androgen receptor blockers (anti-androgens)			
Steroidal	cyproterone acetate	Inhibits androgen receptor (AR) & central nervous system effects	tablet
Non-steroidal -1st generation	bicalutamide flutamide nilutamide	Inhibits AR, thereby reducing the stimulation of PCa cells	tablet
Non-steroidal - 2nd generation	enzalutamide apalutamide	Blocks several steps in the AR signalling pathway: binding to the AR; nuclear translocation of activates receptor; and association of the translocated receptor with DNA	tablet
Adrenal androgen inhibitors	abiraterone acetate + prednisone/ methylprednisolone	Inhibits androgen production at all sources: adrenal glands, testes, tumour	tablet

Abbreviations: GnRH gonadotropin-releasing hormone; LHRH luteinising hormone-releasing hormone

ADT for PCa is associated with numerous and often debilitating adverse effects. The National Institute of Cancer defines an adverse effect as: “an unexpected medical

problem that happens during treatment with a drug or other therapy. Adverse effects may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given. Also called an adverse event."(61). The increasing use of ADT for PCa, the longer timeframe for treatment (an outcome of increased uptake of PSA testing and earlier diagnosis), as well as improved survival and an ageing population, means patients can live for a considerable period of time on, or after, ADT, experiencing these adverse effects(62). While much has been published on the adverse effects of ADT for PCa in recent years, and a number of systematic reviews exist(63-85), some of these do not include current studies or newer ADTs. No single systematic review has previously comprehensively examined the evidence for all adverse effects.

Characterising adverse effects is beneficial for several reasons. Firstly, incidence of adverse effects will provide valuable information for future burden of disease studies and better guide clinical management to reduce symptoms for patients. Secondly, in this era of shared decision making, such information will assist patients to make more informed decisions about their treatment, thus facilitating compliance with their treatment plan and potentially improving disease outcomes. For analysts conducting economic evaluations, inclusion of adverse effect incidence in PCa decision analytic models can provide more comprehensive and accurate information for decision makers. The purpose of this paper, therefore, is to systematically review the current literature on ADT for PCa to identify the highest available level evidence of risk/incidence of common adverse effects. Given the nature of current evidence, this review will comprise a review of existing systematic reviews, supplemented where necessary by evidence drawn from individual studies.

2.2 Methods

Using an *a priori* defined protocol, this systematic review was conducted as per Cochrane guidelines (86). In order to locate the most recent high-level evidence and not duplicate previous research, a systematic search was conducted as outlined below.

2.2.1 Identification - search strategy

A PRISMA compliant systematic search of the literature on the adverse effects of ADT for PCa was conducted for the years 2010-February 2019)(86, 87). Figure 2 shows the search process (identification, screening, eligibility & inclusion). The study screening and selection process consisted of three phases. First, a search was conducted to identify original articles in the following electronic databases: Medline,

Embase, PsycInfo, and Cochrane Library. The search strings comprised terms for PCa, adverse effects and ADT medications (Appendix 1). Where databases allowed, searches were limited to English language, humans. Language limitations were based on review time frames and language capacity of team members; pre-clinical trial research using animals was not relevant to adverse effect incidence, and given the rapidly changing landscape of PCa treatment, a period of ten years of evidence generation was deemed adequate by the research team. A Google Scholar search of adverse effects of ADT for PCa was also conducted.

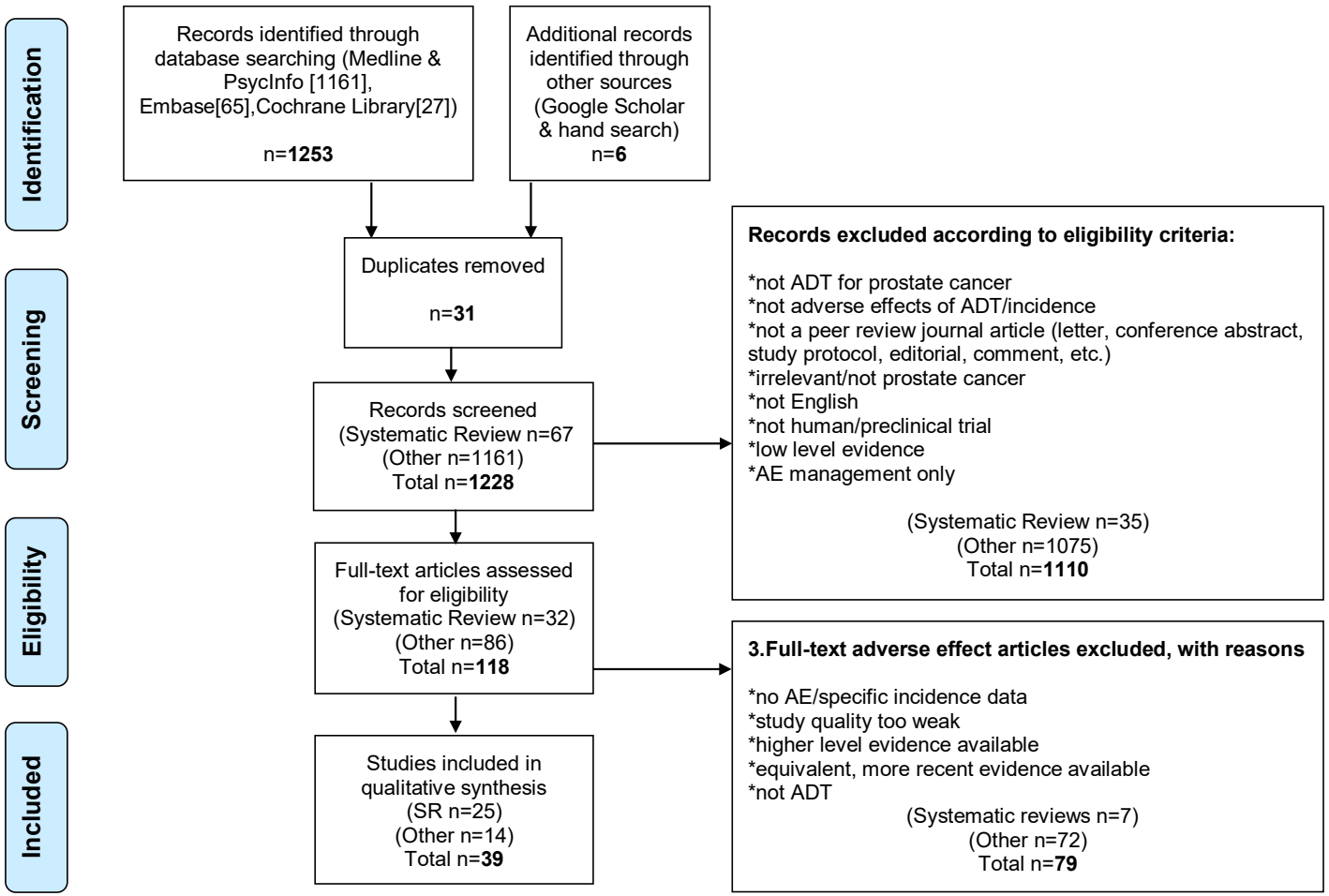


Figure 2 PRISMA flow diagram ADT adverse effects

2.2.2 Classification of studies

Identified studies were then classified using a three-step process.

Step 1: Screening

Titles and abstracts of the retrieved articles were screened following the PICOS criteria in Table 7.

Table 7 PICOS inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Men with PCa receiving ADT	Men with prostate cancer not receiving ADT
Intervention	ADT for PCa	Other forms of PCa treatment
Comparator	No ADT or other PCa treatment	-
Outcomes	Major adverse effects of ADT; incidence, rate or risk	Adverse effects without incidence, rate or risk evidence
Study design	Systematic review, RCT, observational study, population-based study, cohort study	Irrelevant/not PCa; not a peer-reviewed article; descriptive or review article; not English language; does not involve human subjects

Abbreviations: PCa prostate cancer; ADT androgen deprivation therapy; RCT randomised controlled trial

Step 2a: Classification of adverse effect groupings

The remaining records were classified into adverse effect groupings using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0(17) to enable comparison of available evidence for specific adverse effects (Table 8).

Step 2b: Identifying highest level of evidence

In order to have incidence data supported by the highest level of evidence available, classification of articles was guided by the Oxford Centre for Evidence-based Medicine (OECBM) 2011 Levels of Evidence(88, 89). Studies were classified into: A. systematic reviews; B. analytic studies, comprising i) experimental studies such as RCTS and ii) observational studies; and C. descriptive studies. Systematic reviews were prioritised; where they did not provide the evidence required, RCTs were the next level of evidence included. Observational studies were maintained until step three, in the event that higher level studies did not address adverse effect incidence. Descriptive studies were excluded.

The full text versions of the remaining records were obtained and independently assessed for eligibility by two reviewers (KE & HT). Disagreements were resolved through consensus. Where studies of equal quality and evidence level were found, all results were recorded to strengthen the evidence collected. Remaining lower evidence articles were then excluded. The following exclusion criteria were applied with the benefit of full text information: not highest level of evidence available; no incidence information; more recent but equivalent evidence available. Finally, the reference lists of included studies were manually reviewed to identify articles not located by the electronic database search.

2.2.3 Data extraction

Data was extracted from the included studies by one reviewer (KE) and independently reviewed by a second reviewer (HT). For each study, information was recorded on: first author, year and country where study was conducted; sample size and setting; study type, study outcomes or incidence data; and risk of bias or quality assessment.

2.2.4 Methodological quality of systematic reviews and single studies

Quality assessment of included systematic reviews was conducted using the AMSTAR 2, a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both(90). Included individual studies were critically appraised using Cochrane Collaboration recommended tools ROB 2(91) for RCTs and the Newcastle-Ottawa Scale(NOS)(92) for cohort studies(86, 93). Risk of bias or quality ratings were independently assessed by KE and HT to address the possibility of rating error. Any discrepancies were addressed via consensus. Systematic reviews receiving a critically low rating were excluded from the evidence synthesis.

2.2.5 Analysis

Given that the purpose and characteristics of the included individual studies (sample populations, treatment types, PCa stages, patient age, control groups, adverse effect examined and outcomes measured) varied considerably across studies, a meta-analysis was not appropriate for the purposes of this review. Instead, evidence of the highest level available was collected and compared for each adverse effect and a range of scores recorded to ensure the most rigorous incidence data was generated by this systematic review.

2.3 Results

The search of databases located 1,253 records. Google Scholar and a survey of reference lists generated a further six records (n=1,259). Thirty-one duplicates were removed electronically. A total of 1,228 records remained for screening. After preliminary screening of titles and abstracts, 1110 studies that did not match the inclusion criteria were removed. A total of 118 studies remained. Thirty-two full text systematic reviews met the inclusion criteria and were evaluated for adverse effect incidence. Evidence was generated for incidence of body composition changes, bone loss, osteoporosis, metabolic syndrome, diabetes, hypertension, CVD risk, thromboembolisms, hepatoxicity, fatigue, body feminisation, vasomotor flushing, depression, cognitive function and dementia. The remaining single studies (n=86) were then examined for evidence of adverse effect incidence not generated by the

systematic reviews (osteoporosis, hepatotoxicity, gait disturbance, fracture, sexual function) (Table 8). The highest level of evidence generating comprehensive data (e.g. including sufficient stages of PCa and types of ADT) were included in the evidence synthesis for these adverse effects. Thirty-nine studies (25 systematic reviews + 14 individual studies) were judged eligible for inclusion in the review. Detailed information extracted from the 39 studies was recorded in the summary of findings table (Appendix 2).

The following section examines each of the adverse effect sub-groups in turn, summarising study characteristics and adverse effect incidence.

Table 8 Adverse effect groups and evidence consulted for incidence

Group	Adverse effect (CTCAE)	Adverse effect sub-group	Studies (n)
1	Musculoskeletal changes	a) Bone loss b) Osteoporosis c) Fracture	1 (SR) 1 (IS) 8 (IS)
2	Metabolic changes	a) Body composition changes b) Metabolic syndrome c) Diabetes	1 (SR) 1 (SR) 2 (SR)
3	Cardiac disorders	a) Cardiovascular events	11 (SR)
4	Nervous system disorders	a) Cognitive impairment b) Stroke c) Dementia	2 (SR) 3 (SR) 1 (SR)
5	Vascular disorders	a) Hypertension b) Thromboembolic events c) Hot flashes	4 (SR) 2 (SR) 5 (SR)
6	Hepatobiliary disorders	a) Hepatic disorders	2 (SR); 1 (IS)
7	Reproductive system disorders	a) Gynaecomastia and breast pain b) Sexual dysfunction	3 (SR) 2 (SR); 2 (IS)
8	Psychiatric disorders	a) Depression	2 (SR)
9	General disorders	a) Fatigue b) Gait disturbance	3 (SR) 4 (IS)

Abbreviations: SR systematic review; IS individual study; CTCAE Common Terminology Criteria for Adverse Events
Notes: Some studies have multiple adverse effect outcomes so may count more than once

2.3.1 Musculoskeletal changes

1a. Bone loss

ADT increases bone turnover and causes significant, progressive decrements in bone mineral density (BMD) in men with PCa, contributing to an increased risk of osteoporosis and fractures. The magnitude of bone loss rates tends to be higher early in treatment, but also decreases steadily during long term treatment(94). The extent of bone loss differs for measurement site and duration of ADT. One systematic review included five prospective cohort studies of localised or advanced PCa treated with orchiectomy, luteinising hormone releasing hormone (LHRH) agonist or anti-androgen (69). Controls varied across the studies as did treatment duration, with heterogeneity ranging from 82-99%. Pooled analysis of four studies (n=483) determined mean percent bone loss for lumbar spine of -3.6% (95% CI -6.72, -0.47, p=0.02). Five studies (n=515) recorded bone loss for femoral neck of -3.11% (95% CI -4.73, -1.48, p=0.02).

Mean per cent bone loss for total hip derived from four studies (n=483) was -1.59% (95% CI -2.99, -0.19, *p*=0.03)(69).

1b Osteoporosis

ADT induced bone loss is further exacerbated by already high levels of osteoporosis in the ageing population. Studies in UK(95)and US(96) have reported levels of around 40% for osteoporosis and between 40% and 50% for osteopenia in men with PCa initiating ADT. The risk of osteoporosis is heightened by age and comorbidities common in this population. One recent retrospective cohort study conducted in Australia using Pharmaceutical Benefits Scheme (PBS) data involved a 10% random sample of the PCa population receiving their first ADT between 2004 and 2010 compared to a matched population not receiving anti-neoplastic agents or having no comorbidities at baseline(97). There was significant risk of developing osteoporosis in the ADT PCa population: hazard ratio (HR) 1.65 (95% CI 1.48, 1.85). An adjusted HR was also calculated for incidence of osteoporosis stratified by duration of ADT exposure: ≤ 1 year 1.38 (95% CI 1.10,1.72) and > 1 year 1.77 (1.55-2.02)(97).

1c Fracture

Two RCTs and six cohort studies with data on incidence of fractures in men receiving ADT met the inclusion criteria for this review. Two studies focussed on localised PCa; one included recipients of ADT alone, curative treatment and ADT, and orchiectomy(98), the other men received radical prostatectomy or radiotherapy with/without ADT(99). Four studies focussed on advanced cancer, one included only men with non-metastatic PCa receiving any type of ADT or orchiectomy(100), another, men with metastatic PCa comparing gonadotropin releasing hormone (GnRH) agonists with orchiectomy(101), the third, men with advanced cancer receiving intermittent ADT (IADT)(102), and the fourth, men receiving GnRH agonists only with non-metastatic or metastatic PCa(103). Two RCTs examined second generation treatments for non-metastatic(104) and metastatic castrate resistant PCa (CRPCa)(105). These studies established a significant association between ADT and incidence of fracture across the disease spectrum, and identified factors that elevate risk such as age, ADT dose and duration, time from last dose, osteoporosis, metastases and dementia.

2.3.2 Metabolic changes

2a Body composition changes

Body composition changes increase with duration of treatment and comorbidities; they tend to be greater in the first three months and continue over time but less rapidly to six months and longer(67). A meta-analysis by Haseen et al.(67) reported significant changes in body composition for men receiving ADT. Pooled analysis was conducted

from 16 studies (14 cohort and 2 RCTs) which varied in type of ADT and stage of PCa. Analyses included seven studies for increases in body fat mass of 7.7% (95% CI 4.3,11.2, p<0.00001), six for decreases in lean mass of 2.8% (95% CI -3.6, -12.0, p<0.00001), nine for increases in body weight of 2.1% (95% CI 1.35, 2.94, p<0.00001) and eight for increases in body mass index (BMI) of 2.2% (95% CI 1.16, 3.14, p<0.0001). Heterogeneity was quite high across the studies included for each body composition change, 99%, 73%, 55% and 63%, respectively. Sub analyses for ADT type showed that luteinising hormone releasing hormone (LHRH) had greater impact on body composition changes than combination therapy with anti-androgen.

2b Metabolic syndrome

Men receiving ADT tend to experience adverse changes in the following metabolic features: decreased lean mass, increased fat mass (together known as sarcopenic obesity), increased waist circumference, alterations in lipids and decreased insulin sensitivity(106, 107). One systematic review of ADT induced metabolic syndrome incorporated data for meta-analysis from four cohort studies and five cross sectional studies(64). The type of ADT varied across studies from any type of ADT in five studies, GnRH agonist, combined androgen blockade, orchiectomy and anti-androgens in one study and orchiectomy alone in two. The relative risk (RR) of acquiring metabolic syndrome was 75% higher for men with PCa receiving ADT compared to those not receiving ADT (RR 1.75; 95% CI 1.27, 2.41)(64).

2c Diabetes

Two systematic reviews generated data on diabetes incidence. The Bosco *et al.* (64) review mentioned above reported a RR of 1.36 (95% CI 1.17, 1.58) for men receiving ADT. Wang *et al.*(83), pooled data for meta-analysis from four cohort and four cross sectional studies. Incidence of diabetes amongst men receiving ADT (GnRH agonists, combined androgen blockade or orchiectomy) was 10.9% (83). The risk of diabetes was 39% higher for these men than for men not receiving ADT or men on watchful waiting or active surveillance (RR 1.39; 95%CI 1.27-1.53, P<0.001)(83). Sub group analyses for ADT type and duration showed that GnRHa, combined androgen blockade and orchiectomy are significantly associated with risk of diabetes, and longer duration of ADT with elevated risk(83).

2.3.3 Cardiac disorders: Cardiovascular (CV) complications and mortality

Since a large observational analysis of Surveillance, Epidemiology and End Results (SEER) Medicare data demonstrated a significant association between GnRH and incident coronary heart disease, hospital admission for myocardial infarction (MI) and sudden cardiac death in men with PCa, the question of whether ADT increases the risk

of CV events or CV mortality has been raised(108). A systematic review conducted in 2009 showed that ADT is associated with a 17% increased risk of cardiovascular mortality(109). This analysis, however, was based on only two observational studies and two RCTs. Since that time, studies of CV risk for ADT recipients have proliferated and systematic reviews have been conducted of CV risk factors such as hypertension, as well as CV events including MI and CV mortality. While the included systematic reviews focus on CV adverse events, the outcomes measured differ, as do type of ADT, stage of PCa and comparators. Attempts were made to address heterogeneity via pooled meta-analyses, within trial analyses or analyses by study.

There was an increased risk of CV mortality for all types of ADT and for MI or stroke from GnRH agonists, anti-androgens and orchiectomy combined. For ADT type, orchiectomy has the highest risk ratio and anti-androgens(63, 84) or IADT(68, 71) the lowest risk compared to no ADT. The risk for CV events was similar across types of ADT and varied dependent largely on the comparator, as the study by Scailteux shows(80). One systematic review found no significant differences in risk for CV mortality between ADT and controls across all included studies(77). In other reviews, degarelix reduced the risk of CV events compared to GnRHa, as did IADT(68, 71, 81). There was a strong association between grade 3 cardiac adverse events and grade 3/4 vascular events and arbiraterone acetate + prednisone compared to placebo(79). This impact was lower for all grade events. The relative risk of CV events with enzalutamide was lower than that for arbiraterone acetate(85, 110).

2.3.4 Nervous system disorders

4a Cognitive impairment

Two systematic reviews examined incidence of cognitive impairment from ADT(72, 111). Sun *et al.*(82) conducted a meta-analysis of six cohort studies, two of which were prospective and resulted in an odds ratio (OR) of 1.56 (0.50, 4.91, p=0.441). The remaining four retrospective sub-groups included men with senile dementia and Alzheimer's disease, and while the risk of cognitive impairment was higher, it was not statistically significant (HR 1.28; 95% CI 0.93, 1.76 p=0.130). They concluded that results could not reliably confirm the relationship between ADT and cognitive impairment. A second meta-analysis of 14 studies suggested that for men receiving ADT for PCa, there was insufficient evidence to support cognitive decline with the exception of compromised visuomotor skills, where a significant decline was reported. The weighted average effect was -0.67 (95% CI -1.17, -0.17; P=0.008)(72). The extent of the deficit was also larger with shorter time to follow-up. However, there was insufficient evidence to determine whether these deficits were primarily motor related,

that is arising from ADT related muscle loss, or evidence of low testosterone related deficits in visuospatial skill. The authors concluded that ADT recipients can expect cognitive functioning to be similar to that of men with PCa not receiving ADT and men without PCa, however, clinicians and patients need to be aware of the potential for visuomotor impairment when deciding on treatment(72).

4b Stroke

Two meta-analyses were conducted to determine incidence of stroke. Meng et al.(73) found a significant association between stroke and some types of ADT. Pooled analyses of GnRH alone resulted in a HR of 1.20 (95% CI 1.12, 1.28, *P*<0.001); GnRH + anti-androgen, a HR of 1.23 (95% CI 1.13, 1.34, *P*<0.001); and orchiectomy a HR. 1.37 (1.33-1.46, *P*<0.001). The HR for all ADT showed a higher incidence for ADT recipients compared to control groups, (HR1.12; 95% CI 0.95, 1.32), but no significant association. Another meta-analysis conducted pooled analyses of a range of different types of ADT showing a significant association between stroke and ADT(80). For example, in the only RCT, RR of GnRH agonist compared to GnRH antagonist was 3.44 (95% CI 0.22, 1.32). In observational studies, results varied considerably between different types of ADT with greater relative risk for GnRH agonists and orchiectomy compared to anti-androgens and combined androgen blockade (CAB).

4c Dementia

Men receiving ADT have increased circulating β-amyloid protein levels, the accumulation of which characterizes Alzheimer's disease(75). Men diagnosed with dementia tend to have lower testosterone levels and impaired cognitive function, which for recipients of ADT, has been noted from as early as six months post treatment initiation(75). One systematic review conducted a meta-analysis of studies reporting any dementia outcome showed an increased risk associated with ADT (HR 1.47; 95% CI 1.08, 2.00; *p*= 0.02). Studies reporting all cause dementia and Alzheimer's disease were also analysed separately resulting in hazard ratios of 1.46 (95% CI 1.05–2.02; *p*<0.001) and 1.25 (95% CI 0.99, 1.57; *p*<0.06), respectively. Current evidence thus suggests that ADT may be associated with an increased risk of dementia(75).

2.3.5 Vascular disorders

5a Hypertension

Hypertension is one of the strongest risk factors for all CV diseases and is strongly associated with age. ADT, particularly second generation hormonal agents such as abiraterone acetate and enzalutamide, is associated with significant increases in risk of hypertension. Four systematic reviews generated data on the incidence of hypertension for men receiving ADT for PCa (78, 85, 110, 112). One showed a higher

incidence of long-term hypertension with radiotherapy and GnRH agonists than with the use of anti-androgens (12% vs 4%)(112). Arbiraterone acetate and enzalutamide compared to placebo or other forms of ADT was associated with a high risk of hypertension higher than that for CV events in three systematic reviews (78, 85, 110).

5b Thromboembolic events

Population-based studies of men receiving ADT for PCa have revealed an association between ADT and increased risk of thromboembolic events such as deep vein thrombosis (DVT) and pulmonary embolus (PE). Two meta-analyses examined the evidence for ADT associated thromboembolic events(66, 74). One restricted the analysis to five cohort studies which compared GnRH agonists alone, GnRH agonists + anti-androgens, anti-androgens alone and orchiectomy with no ADT(66). In this meta-analysis, DVT was significantly associated with GnRH agonist alone (HR 1.47; 95% CI 1.07, 2.03 p=0.017), GnRH agonist + anti-androgen (HR 2.55; 95% CI 2.1, 2.94, p<0.001) and anti-androgen alone (HR 1.49; 95% CI 1.13, 1.96, p=0.004), but not with orchiectomy (HR 1.80 95% CI 0.93, 3.47, p=0.07). Pulmonary embolism was significantly associated with GnRH agonist alone (HR 2.26; 95% CI 1.78, 2.86, p<0.001) and orchiectomy (HR 2.12; 95% CI 1.44, 3.11, p<0.001)(66). The other systematic review included oestrogens in addition to the above-mentioned forms of ADT and drew evidence from 20 studies comparing ADT with no ADT, short term ADT and IADT(74). In this meta-analysis, ADT without oestrogen in 10 studies caused a significant increase in risk of thromboembolic events (RR 1.43; 95% CI 1.15, 1.77, p<0.001) as did oestrogen alone in 9 nine studies (RR 3.72; 95% CI 1.78, 7.80, p<0.001). Sub analyses comparing disease stage demonstrated a significantly increased risk of thromboembolic events from ADT without oestrogen and oestrogen alone for both localized (RR 1.10; 95% CI 1.05,1.16, p=<0.001) and metastatic disease (RR 1.58; 95% CI 1.24, 2.03, p <0.001), but not for studies of continuous vs intermittent ADT. Sub analyses examining impact of ADT duration showed a significantly increased risk of thromboembolic events for duration >12months. Significant heterogeneity was resolved in ADT without oestrogen analysis for localized disease (0%) but not for the metastatic disease analysis (84%) or the oestrogen only analysis (71%)(74).

5c Hot flashes

Five systematic reviews referred to incidence of vasomotor flushing across various treatments and stages of PCa from locally advanced to metastatic CRPCa(70, 71, 81, 85, 112). Anti-androgens have a significantly lower risk of flashing than orchiectomy (RR 0.23; 95% CI 0.10, 0.27)(70) and GnRH agonists (<1% vs 45%)(112). Enzalutamide has a significantly increased risk of flashing compared to bicalutamide or

placebo (RR 1.94; 95% CI 1.55, 2.42)(85). There was no significant difference in flashing between CADT and IADT(71) or between degarelix and GnRH agonists(81).

2.3.6 Hepatobiliary disorders

Two systematic reviews examined incidence of hepatotoxicity; one from ADT + abiraterone acetate + prednisone compared to placebo for metastatic hormone sensitive PCa (HR 3.09; 95% CI 2.12, 4.50, *P*<0.001)(79), and one from abiraterone acetate + prednisone compared to placebo for CRPCa (all grade RR 1.93; 95% CI 1.15, 3.24, *p*=0.01 & high grade RR 2.94; 95% CI 0.95, 9.08, *p*=0.06) (78). A large population-based study (n=82,938) using SEER-Medicare data for 1992-2009 found a significantly increased risk of any liver disease (HR 1.47, 95% CI 1.35, 1.60), non-alcoholic fatty liver disease (NAFLD) (HR 1.54, 95% CI 1.40, 1.68), liver cirrhosis (HR 1.35, 95% CI 1.12, 1.60), and liver necrosis (HR 1.41. 95% CI 1.15, 1.72) for men with PCa receiving GnRH agonists and antagonists(113).

2.3.7 Reproductive system disorders

7a Gynaecomastia and breast pain

Gynaecomastia and breast pain are common adverse effects of non-steroidal anti-androgen therapy (bicalutamide, flutamide), and less so, GnRHa therapy, that can seriously impact men's masculinity and quality of life(65, 114). Three systematic reviews analysed the incidence data(70, 71, 112). Two studies reported that, compared to GnRH agonists, non-steroidal anti-androgen therapy was associated with a significantly increased risk of gynaecomastia (RR 8.43; 95% CI 3.19-22.28)(70) and 70% vs 11%(112). One of these studies also reported a 23 fold increased risk of breast pain pooled from eight studies (RR 22.97; 95% CI 14.79, 35.67)(70). There was a lower risk of gynaecomastia for IADT compared to CADT (RR 0.63; 95% CI 0.36, 1.10) but the difference was not statistically significant(71).

7b Sexual dysfunction

Sexual dysfunction, which here refers to erectile dysfunction and decreased libido, is a common and often distressing experience for both men receiving ADT for PCa and their partners. Two systematic reviews included RCTs with incidence of sexual dysfunction or decreased libido, one comparing erectile dysfunction between degarelix and GnRH agonists (RR 0.94 95% CI 0.700, 1.26, *p*=0.686)(81), the other IADT and continuous CADT for erectile dysfunction (RR 1.03; 95% CI 0.74, 1.43) and decreased libido (RR 1.01; 95% CI 0.95, 1.07) (71). No significant differences were found for erectile dysfunction or decreased libido between types of ADT. There is a paucity of data on sexual dysfunction, however, two RCTs examined the effect of short-term neoadjuvant ADT before radiotherapy and compared ADT recipients to those receiving

radiation only, reported significant declines in sexual function from two months ADT administration(115, 116). Daly et al.(115) compared duration of ADT; 54% of men in the 4-month arm and 39% in the 8-month arm, who had sexual function at baseline, retained sexual function at one year. There were no statistically significant differences between arms and smaller decreases in sexual function were recorded after one year(115). This study found that 26% of men can expect to retain erectile function five years after receiving three or four months of ADT with age the only significant risk factor(115). Similar results were obtained in a second RCT comparing men receiving neoadjuvant ADT and radiotherapy and those receiving radiotherapy alone. There was a statistically significant difference between arms: number of men who always or almost always had erectile function at baseline in the ADT arm decreased by over 50% one year after ADT initiation(116).

2.3.8 Psychiatric disorders: Depression

Depression and anxiety are often unaddressed adverse effects among patients with PCa and are associated with increased health service use, costs and mortality(117-119). Two systematic reviews examined the incidence of depression among men with PCa receiving ADT(71, 76). One conducted a pooled analysis of 18 studies, both prospective and retrospective, involving a variety of forms of ADT from primary anti-androgen, radiotherapy or radical prostatectomy plus adjuvant ADT, and orchiectomy. Comparators included lesser exposed ADT group (e.g. no ADT, short term ADT or IADT). Relative risk of depression was 1.41 (95% CI 1.18-1.70, p<0.001) (76). The second systematic review analysed 15 RCTs of which three generated evidence of depression experienced by recipients of continuous and intermittent ADT and found no significant difference between IADT and CADT (RR 0.91; 95% CI 0.39, 2.13)(71).

2.3.9 General disorders

9a Fatigue

Two systematic reviews examined the incidence of fatigue for men receiving ADT for PCa. One conducted a pooled analysis of all stages of PCa and found no significant difference between IADT and CADT, but an incidence of fatigue that favoured IADT (HR 0.94; 95% CI 0.60, 1.48)(71). However, for men receiving new hormonal agent-based therapies for metastatic CRPCa, enzalutamide or arbiraterone acetate, fatigue is one of the most common adverse effects. A significant difference in incidence was discovered from pooled analyses of both all grade (RR 1.27; 95% CI 1.13, 1.43) and grade 3 or greater fatigue (RR 1.25; 95% CI 0.92, 1.71, p=0.02)(120).

9b Gait disturbance, physical function and falls

Clinically meaningful declines in physical functioning occur within 3-6 months after ADT initiation and stabilise or worsen over time(40, 121, 122). Alibhai et al.(121) report that for each 5-kg reduction in grip strength over 4 years, there was a 24% increased mortality risk, and with each 5% loss of relative grip strength, a 6% increased mortality risk. In a secondary analysis of this same population, the incidence of falls was higher for men receiving CADT, with a trend towards increased risk (p=0.083)(123). Graff et al.(124) conducted a sub-group analysis (≥75 years) of participants in the PREVAIL RCT, where there was a much higher incidence of falls, suggesting enzalutamide may further increase the risk of falls because all men in the trial were receiving ADT. In a Phase III, double-blinded RCT examining apalutamide versus placebo, Smith found a higher incidence of falls for participants receiving apalutamide(104).

2.3.10 Methodological quality of included studies

Systematic reviews

Twenty-five systematic reviews (24 incorporating a meta-analysis) were assessed using the AMSTAR 2 tool (Appendix 3). Confidence in overall results of the review rating varied, 10 were rated as low, 11 as moderate, and four as high. Results were impacted by lack of data or diversity of studies available. ADT is used broadly across the spectrum of PCa, so patient characteristics differ as do the type and duration of ADT administration. In addition, studies involved different comparators or control groups, making comparison across studies difficult. Heterogeneity between studies within reviews was often quite high. Risk of bias or quality assessments were not always conducted or just not reported in lower rated studies, despite their critical importance. Similarly, publication bias was overlooked in a number of reviews. Overall, systematic reviews brought together a comprehensive collection of the best available evidence on the adverse effects of ADT for PCa and provide a sound evidence base.

Randomised Controlled Trials

Four RCTs were assessed for risk of bias using the ROB-2 tool generating ratings such as low, some concerns, or high risk of bias (Appendix 4). Three of the four trials rated an overall low risk of bias and two of these were studies based on well-known trials (ICORG 97-01; PREVAIL); all four were published in high ranking journals by recognised authors/clinicians in the PCa field, however, all four also had varying degrees of conflict of interest from author association with pharmaceutical companies.

Cohort studies

Ten cohort studies were assessed for quality using the Newcastle Ottawa Scale (NOS) for a possible rating of good, fair or poor (Appendix 5). All achieved a rating of

good and only three had weaknesses which were not considered sufficient to require a downgrading, given their other strengths. One study had missing outcome data that was not addressed and no measures to prevent confounding from previous falls or exercise(123); another had a 40% loss to follow up(121) and the third matched their experimental and control cohorts for age and no prior comorbidity only(97).

2.4 Discussion

This comprehensive systematic review of adverse effects (n=19) of ADT for PCa confirms that many are commonly experienced by patients and survivors. A broad spectrum of ADT is represented, comprising GnRH agonists, GnRH antagonists, anti-androgens (steroidal and non-steroidal) and combinations of these drugs or neoadjuvant and adjuvant therapy with curative treatments like RP or RT. Intermittent ADT is also represented. Second generation non-steroidal anti-androgens, abiraterone acetate and enzalutamide, figured strongly in the systematic reviews. Statistically significant increased risks were evident in all the most common adverse effects from the CTCAE groupings (musculoskeletal, metabolic, cardiac, nervous system, vascular, hepatobiliary, reproductive system, psychiatric and general disorders). The dominant factor across all adverse effect incidence was type of ADT.

For musculoskeletal events duration of ADT was also a factor; for fractures, ADT dose, age, presence of osteoporosis, metastases and dementia impacted on incidence. ADT impacted combined CVD morbidity and the risk of specific CV diseases such as myocardial infarction and ischaemic heart disease. Risk was associated with type(63, 84), adverse event grade(78, 79, 85) and duration of ADT(125). Cardiac mortality was less common but increased risk was identified for all ADT, ADT monotherapy and GnRH agonists(84). Increased risk of stroke was associated with orchiectomy, CAB and GnRH agonist alone(73). There was also a significant association between ADT and hypertension, particularly for second generation therapies, abiraterone and enzalutamide. Other vascular disorders like thromboembolic events also showed a significant association with GnRHa alone, CAB, anti-androgen alone, oestrogen and orchiectomy(66, 74). For vasomotor flashing, enzalutamide had a significant increased risk and anti-androgens a significantly lower risk than other types of ADT (70, 71, 81, 85, 112). GnRH agonists and antagonists showed a strong association with hepatotoxicity(113), as did abiraterone acetate, two to three times higher than placebo for men with CRPCa(78, 79).

Reproductive disorders were common with significantly increased risk of gynaecomastia and breast pain for anti-androgens over GnRH agonists(70, 112). Sexual function was significantly impacted by ADT with only 26% of men expected to

retain some sexual function five years from initiation of ADT(115). There was no evidence to suggest a significant difference in relation to type of ADT(71, 81). The impact of ADT on the risk of depression was confirmed in the systematic review by Nead *et al.* which showed a 40% higher risk of depression for men receiving ADT which, like sexual function, was associated with exposure (76). Fatigue is a complex adverse effect associated with many cancer treatments but for men receiving enzalutamide and abiraterone for PCa, there was a 27% greater risk of fatigue and a 50% greater risk for prechemotherapy men initiating ADT(120). Potentially related to fatigue and other adverse effects, declines in physical function and higher incidence of falls were also associated with ADT, significantly more-so with enzalutamide(124) and apalutamide(104).

Cognitive disorders were the exception amongst the adverse effect groupings with an inconclusive result from two systematic reviews(72, 82). Similarly, the systematic review of dementia suggested only that there may be an association between ADT and risk of dementia(75). Interestingly, McGinty *et al.* found a statistically significant increased risk associated with visuospatial cognitive skills, suggesting a possible link to increased incidence of falls and fractures for this population(72). Such a broad range of adverse effects, some with high levels of incidence, poses problems, not only for the patient and their family who bear the consequences of increased morbidity or mortality and reduced quality of life, but also for society. There are significant cost implications of suffering these adverse effects in the form of their management, supportive care and increased health services utilisation, without considerations of productivity losses for those men in this population still actively employed or their carers. Management of adverse effects can take a number of forms from medications or counselling to exercise interventions; each involving increased resource utilisation as well as out of pocket costs for the patient.

In recent years, interest in adverse effects has increased, evidenced by the number of systematic reviews included in this review. There is growing awareness of the impact of many of these adverse effects on the part of clinicians, patients, economists and decision makers, from both a quality of life and a cost perspective. Bourke et al. raised the need for clearly defined adverse effects, in order that a better understanding of potential risks and subsequent treatment costs is developed to accurately inform the costs and effects associated with these drugs(126). Pearce et al. make a similar point, advising that economic evaluations should include all adverse effects regardless of severity(127). While the adverse effects associated with ADT are many, varied and complex, it is important that economic evaluations include consideration of them to

ensure models are developed that accurately reflect the impact of adverse effects on drug cost-effectiveness, particularly given the current emphasis on personalised care.

No single systematic review has previously provided such a comprehensive review of this topic. This review, conducted and reported following Cochrane guidelines, updates the current knowledge across all common adverse effects of ADT for PCa(86). We employed an *a priori* designed protocol and carried out an extensive literature search using multiple databases, Google Scholar and bibliographic hand search. Methodological quality of included studies was assessed using three Cochrane approved instruments and, with few exceptions, provided moderate to strong evidence of ADT adverse effects. This systematic review also includes new ADT medications like apalutamide, enzalutamide and abiraterone acetate, and through the weight of recent evidence, confirms effects previously considered contentious, such as cardiovascular toxicity, or rare, such as hepatotoxicity.

This review was limited by available data; while the full range of PCa stages from localized to metastatic CRPCa were represented, not all types of ADT or all stages of PCa were captured for all adverse effects, particularly for newer therapies. Studies were characterised by considerable heterogeneity in study design, aims, outcomes, sample size, exclusion criteria, geographical location, number of sites involved and length of follow up. While all study participants were men with PCa receiving ADT, there was considerable variation between and across studies in relation to age, PCa stage, treatment, comorbidities, and demographics. Heterogeneity was not always addressed in meta-analysis. While a rigorous search of the literature was conducted, it is possible that not all studies reporting the adverse effects of ADT for PCa were identified.

2.5 Conclusion

This review provides the first comprehensive incidence of the most common adverse effects of ADT for PCa based on currently available evidence. These findings are significant for clinicians, researchers, health providers, health economists, PCa patients, their carers and society. It is evident that more research is needed in adverse effects of ADT for PCa; questions also remain in terms of potential recovery and management. It is hoped this review will assist in stimulating further questions and research around adverse effects, as well as the development of suitable interventions to decrease their risk. These findings also highlight the importance of supportive care for PCa patients receiving ADT and their carers. Consideration of adverse effects and their management in economic evaluations of PCa treatment is also important, particularly given their potential to add further costs to what is already costly treatment.

Chapter 3 The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review

3.1 Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in Australian men, accounting for one quarter of all new cancer diagnoses for males (128). With a predicted 5-year global prevalence of 3.7 million in 2018 and an incidence of 18,274 in Australia alone, PCa represents a considerable public health burden (129). The cost of PCa in Australia has been estimated at US$270.9 million in 2016, rising to US$384.3 million by 2025 (130). Androgen deprivation therapy (ADT) is the standard first-line therapy for metastatic PCa but also improves survival in men with high-risk localised, locally advanced and castrate resistant PCa. Thus, ADT is used across much of the spectrum of disease, often for considerable periods of time (16). Debilitating adverse effects are a significant and largely unavoidable feature of ADT for men with PCa. A recent systematic review (131) identified 19 adverse effect sub-groups classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (17). Statistically significant increased risks were evident for all nine ADT adverse effect groups (musculoskeletal, metabolic, cardiac, nervous system, vascular, hepatobiliary, reproductive, psychiatric and general disorders), with evidence of increased risks for 17 out of the 19 sub-groups (131). Cognitive disorder and dementia were the exceptions, with inconclusive results or suggested associations with ADT only, based on currently available evidence(131). Given the incidence of these adverse effects, there is a need for management strategies that minimise the burden of PCa treatment with ADT. The potential for multiple simultaneous adverse effects, the impact these have on cancer outcomes and quality of life, as well as their associated management, are important considerations in the treatment and supportive care of men with PCa. While the value of exercise as medicine has long been acknowledged for the general population (132) as well as cancer (47, 48) and PCa populations (32, 37), it is increasingly being recognized as an efficacious strategy in managing the adverse effects associated with cancer treatment.

In 2019, the Exercise and Sports Science Australia (ESSA) position statement and the American College of Sports Medicine (ACSM) guidelines were updated with current scientific evidence, clinical experience and exercise science principles. They emphasise the importance of an appropriate exercise prescription for cancer patients, which is individualised and targeted for the specific health issues most impacting the patient (50, 51). The ACSM guidelines for cancer survivors recommend moderate intensity aerobic training at least three times per week, for at least 30 minutes. The

addition of resistance exercise to aerobic training, at least twice a week, using at least two sets of eight to 15 repetitions, results in similar benefits, though evidence suggests resistance training alone may not be enough (51). The ESSA guidelines recommend a more tailored approach with exercise mode and dosage prescribed specifically to ameliorate, in priority order, the health issues and mortality risks of greatest concern for the patient. Both these documents were based on extensive evidence reviews to ascertain the strength of evidence supporting the use of exercise for cancer patients and survivors. Strong evidence was available for a number of cancer-related outcomes: anxiety and depression, fatigue, health related quality of life (HRQoL) and physical function. Moderate evidence was also available for bone health and sleep. While organisations such as the American Society of Clinical Oncology (ASCO)(133), the National Comprehensive Cancer Network (53) and the National Institute for Care and Excellence(54) have PCa survivorship guidelines that support exercise for adverse effect management, there is no comprehensive review of the benefits of exercise in managing the adverse effects of ADT for PCa. Therefore, the aim of this review is to identify existing evidence of the benefits of exercise in managing the adverse effects of ADT for PCa.

3.2 Methods

A rapid review of the literature was undertaken by the authors to examine the role of exercise in the management of ADT adverse effects outlined above (131). A search was conducted in Medline, PsycINFO, Google Scholar and Google for the years 2010 to September 2019. A period of ten years of evidence generation was chosen by the research team in order to focus on more current treatment regimes and approaches to management. Search terms comprised: androgen deprivation; prostate cancer; adverse effects; adverse events; toxicity; complications; management; guidelines; and exercise; or physical activity. The Population, Intervention, Comparator and Outcome (PICO) inclusion and exclusion criteria are outlined in Table 9. Evidence was prioritised according to the Oxford Centre for Evidence-based Medicine (OECBM) 2011 Levels of Evidence (88) and included: A. systematic reviews; and B. analytic studies, such as randomised controlled trials (RCTs). Where little or no evidence of the effect of exercise was available for men with PCa receiving ADT for a particular adverse effect, a subsequent search was conducted to identify evidence of exercise impact for other cancer patients, disease specific evidence (e.g. diabetes or cardiovascular disorders) or evidence from the general population. This required removing prostate and androgen deprivation from the search terms and including other terms relevant to ADT adverse effects like hormone therapy, cardiovascular, diabetes, metabolic, depression,

falls, fractures, cognitive, dementia, hot flushes, deep vein thrombosis and liver disease. PICO inclusion criteria were also broadened. The population parameter included the general population and other disease risks; the intervention parameter other adverse effects or disease risks; and the outcomes parameter adverse effect or disease risk management. The comparator parameter was maintained. PICO exclusion criteria remained the same with the exception of the population parameter which was changed to younger people (<50 years). Qualitative judgments of currently existing evidence were based on agreement between authors due to the heterogeneity of sources and paucity of evidence in some areas.

Table 9 PICO inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Men with PCa receiving androgen deprivation therapy ADT	PCa population not receiving ADT
Intervention	Supervised or prescribed exercise to manage ADT adverse effects for PCa	Unsupervised or purely recreational exercise (i.e. without prescription or professional oversight)
Comparator	No management, pharmaceuticals or medical treatment only	-
Outcomes	ADT adverse effect management (higher levels of evidence: Systematic Review, Meta-analysis, RCT, cohort study, population-based observational study)	Lower ranked evidence (e.g. review, cross sectional study)

Abbreviations: ADT androgen deprivation therapy; PCa prostate cancer; RCT randomised controlled trial

The adverse effects of ADT were classified according to the CTCAE (17) sub-groups to facilitate comparison of available evidence for specific adverse effects (131). Evidence of the role of exercise in addressing each of these adverse effect sub-groups is described below.

3.3 Results: Effectiveness of exercise in managing adverse effects of ADT

Results will be presented in two sections. Section 1 will present the evidence for the role of exercise in managing the adverse effects of ADT. Section 2 will provide evidence from other populations for the role of exercise in managing other adverse effects or disease risks, where there is little or no evidence for the PCa population.

3.3.1 Musculoskeletal changes

1a Bone loss, 1b osteoporosis and 1c fracture risk

Management of bone loss, osteoporosis and fracture risk consists of baseline assessment of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA) of the spine, hips and forearm, which should then be followed by lifestyle interventions comprising exercise and diet, and pharmacological treatment with bisphosphonates only if required (23). Resistance exercise training and high impact loading exercises help to mitigate ADT related bone loss, thus improving bone health and reducing fracture risk. While one systematic review and meta-analysis of the most

effective methods for preventing osteoporosis in men taking ADT for PCa concluded exercise alone was insufficient to address bone loss(134), improvements in or preservation of BMD for men with PCa receiving ADT who participated in an exercise intervention have been reported in three recent RCTs (135-137). These studies reported improvements in hip and/or spine BMD (where the most problematic fractures occur). Endurance and resistance exercise improved bone mineral density in the right and left total hip and right and left femur in one study (136), combined resistance, aerobic and impact loading exercise improved lumbar spine BMD in another study (135), and combined impact loading and resistance exercise attenuated the decline in both spine and hip BMD in another (137). These findings highlight the impact of targeted exercise and are critical for a population at high risk of falls and fractures (131).

3.3.2 Metabolic changes

2a Body composition

Androgen deprivation therapy causes increased fat mass and decreased lean mass possibly progressing to sarcopenic obesity in many men with PCa. Increased abdominal fat promotes insulin resistance and reduced lean mass contributes by reducing glucose uptake in muscles. Visceral obesity has also been associated with increased fatigue (138), reductions in BMD and bone strength and the potential, if not managed, to impact adversely on other disease risks, morbidity and mortality. An intensive lifestyle intervention should be instituted to prevent weight gain and worsening insulin resistance (23). Exercise has been shown to be effective in improving body composition in seven systematic reviews (49, 139-144). Outside these systematic reviews, evidence of exercise induced reductions in fat mass were reported in one RCT (145), and evidence for increased lean mass and/or muscle strength in four RCTs (135, 137, 146, 147).

2b Metabolic syndrome

Metabolic syndrome requires similar management strategies to its individual features such as obesity/weight gain (increased waist circumference), hyperglycemia (increased fasting glucose), hypertriglyceridemia (increased triglycerides), decreased serum high density lipoprotein (HDL), increased insulin and hypertension. Importantly, close monitoring and intervention is recommended, particularly in the first year of ADT, because adverse effects can occur from three months post treatment (22, 148) and there are subsequent risks associated with diabetes and cardiovascular health. Exercise and lifestyle change are important considerations in addressing these risks. Results from one systematic review on the effect of exercise for men receiving ADT

reported inconclusive results for cardiometabolic risk markers (49).

2c Diabetes

Diabetes risk is a serious concern for PCa survivors receiving ADT due to the effect of ADT on insulin sensitivity and other CVD risk factors. Exercise is recognised as a critical tool in the prevention and treatment of diabetes (149-151), however, no PCa specific evidence exists in relation to the effect of exercise in mitigating diabetes.

3.3.3 Cardiac disorders

3a Cardiovascular events

Androgen deprivation therapy is associated with elevated cardiovascular (CV) morbidity or mortality, and given the aforementioned metabolic effects of ADT and associated CV complications, it is advisable that patients receiving ADT undergo metabolic evaluation at baseline and periodically during follow-up visits (152). There is, however, a paucity of consistent data on the impact of exercise on these outcomes for men receiving ADT for PCa. Only one systematic review included evidence in relation to PCa survivors, which showed exercise training is associated with significant improvements in vascular endothelial function and peak oxygen volume (VO_2) (153). Improvements in flow-mediated dilation (FMD) are associated with improved CVD risk independently of more traditional risk factors such as body mass index (BMI), cholesterol or blood pressure (153). The effect of exercise on change in FMD (1.3%) was similar to that reported for other healthy and diseased populations (153).

3.3.4 Nervous system disorders

4a Cognitive impairment

While the suppression or blocking of testosterone by ADT is likely to increase cognitive decline, there is a lack of conclusive evidence in relation to the deleterious effect of ADT on cognition, especially verbal, spatial and executive functioning; thus, there is no definitive recommendation for preventing or treating cognitive impairment in men with PCa (131). Age, stage of disease and co-morbidities may contribute to cognitive changes in patients on long-term ADT (154). While evidence exists to show that exercise improves cognitive function in the general population, this has not been demonstrated in PCa patients receiving ADT.

4b Stroke

Little evidence exists in relation to the impact of exercise in reducing risk of stroke or its management specifically for men with PCa receiving ADT outside improved endothelial function as for cardiovascular disorders above (153).

3.3.5 Vascular disorders

5a Hypertension

Androgen deprivation therapy, particularly second generation hormonal agents such as abiraterone acetate and enzalutamide, is associated with significant increases in risk of hypertension (131). While there is currently no evidence of the impact of exercise on hypertension for men with PCa receiving ADT, regular screening and lifestyle modification (including exercise and diet) are recommended (23).

5b Thromboembolic events

While there is evidence of an association between ADT and increased risk of thromboembolic events such as deep vein thrombosis (DVT) and pulmonary embolus (PE) (131), no PCa specific evidence currently exists for the role of exercise in mitigating this effect.

5c Hot flashes

There is an established association between ADT and vasomotor flushing across various treatments and stages of PCa from locally advanced to metastatic castration resistant prostate cancer (mCRPCa) (131). Exercise could potentially benefit men with PCa receiving ADT and experiencing hot flashes, however, no evidence currently exists, and more research is needed.

3.3.6 Hepatobiliary disorders

Arbiraterone acetate and gonadotropin-releasing hormone (GnRH) agonists are both associated with an increased risk of hepatotoxicity (131). Currently, there is no evidence for exercise as a mitigating strategy specifically for men receiving ADT for PCa.

3.3.7 Reproductive system disorders

7a Gynaecomastia and breast pain

Gynaecomastia and breast pain or mastalgia, often referred to in the literature as breast events, are a common adverse effect of non-steroidal antiandrogen therapy (bicalutamide, flutamide) and, while less common for GnRH agonist therapy, can seriously impact men’s masculinity and quality of life (65). There is no evidence to support the use of exercise as a strategy to manage gynaecomastia in men with PCa receiving ADT.

7b Sexual dysfunction

The adverse effects of ADT that relate to sexual dysfunction can result in a perceived loss of masculinity and difficulties in the relationship dyad. Qualitative research conducted alongside a RCT which involved interviews with PCa patients

found that exercise reinforces masculinity and thus enhances sexual wellbeing (155). Evidence from one systematic review (143) and one RCT indicates exercise can enhance sexual health following PCa treatment and exercise initiated with treatment can help to maintain sexual function in men who were sexually active prior to commencing ADT (156).

3.3.8 Psychiatric disorders

8a Depression and anxiety

A PCa diagnosis is a major source of life stress for most men and treatment can exacerbate this effect, contributing to significant decrements in quality of life. Age, cancer stage, comorbidities, psychological disposition, self-efficacy, even marital status, can impact on the nature and severity of this effect(157). From a physiological perspective, exercise causes alterations to hormones (e.g. endorphin and monoamine levels), corticosteroids, pro-inflammatory cytokines, growth factors and neurogenesis, impacting mood and cognitive function and in this way may contribute to improvements in mental wellbeing(157). Systematic review evidence shows exercise improves quality of life (including mental health domains) in the PCa population (141, 158, 159).

3.3.9 General disorders

9a Fatigue

In recent years, there has been recognition of the need to address the debilitating effects of cancer related fatigue. Strong evidence from eight systematic reviews (49, 140, 141, 160-164) and one RCT (165) support the effectiveness of exercise in addressing fatigue during and after treatment with ADT for PCa. Moderate intensity aerobic exercise and combined aerobic and resistance programs had significant effects, with moderate to vigorous exercise most effective.

9b Gait disturbance

Functional decline is one outcome of the ageing process and ADT for men with PCa can exacerbate this decline and result in frailty that impacts significantly on activities of daily living (ADLs) and quality of life (166). Strong evidence from eight systematic reviews (49, 139-142, 144, 160, 163) and two RCTs (145, 147) not elsewhere included, supports the efficacy of exercise in addressing the functional decline associated with ADT. Men with PCa undergoing ADT benefit from exercise training, demonstrating consistent, positive results in physical and muscular performance.

3.4 Results: Effectiveness of exercise in managing adverse effects or disease risks in other populations

3.4.1 Musculoskeletal changes

Strong evidence for the effectiveness of exercise in addressing the adverse effects of ADT for PCa is currently limited, however evidence often exists in other populations. This is the case for the musculoskeletal adverse effect, fractures. Sherrington et al. (167) conducted a comprehensive systematic review of the effectiveness of exercise interventions in preventing falls in older people (i.e., older than 60 years) living in the community and found reductions in falls and fall-related fractures.

3.4.2 Metabolic changes

While results for ADT induced metabolic changes are inconclusive in the PCa population, a large meta-analysis of RCTs conducted in the general population demonstrated that exercise training significantly improved CVD biomarkers of lipid and lipoprotein metabolism, glucose intolerance and insulin resistance, systemic inflammation, and hemostasis. The effects of exercise on cardiorespiratory fitness measures also showed that people with type 2 diabetes, hypertension, hyperlipidemia or metabolic syndrome appeared to benefit more from exercise. Significant modification of effects on total cholesterol and low density lipoprotein cholesterol (LDL-C) were also observed for people with these conditions (168).

A number of systematic reviews report the importance of exercise for people with diabetes(168-171). Resistance exercise improves insulin sensitivity and glucose tolerance, while improving lean body mass and strength parameters. Both resistance and aerobic exercise can assist with management of blood glucose levels, lipids, blood pressure, cardiovascular risk, mortality and quality of life (168-171).

3.4.3 Cardiac disorders

The effect of exercise on cardiovascular toxicity resulting from cancer treatment is an emerging discipline (51, 172). Poor cardiorespiratory fitness is associated with a higher risk of treatment toxicity, higher symptom burden and increased risk of all-cause and cancer specific mortality in cancer patients, but is not recognized as a traditional CVD risk (172). The importance of vascular adaptation to exercise and the impact on cardiovascular risk in the general and CVD populations is increasingly being recognized (173, 174). A systematic review and meta-analysis of lifestyle modification programs for patients with coronary heart disease showed that comprehensive programs reduced mortality by 34% and re-incidence and re-admission rates by 35% over follow-up of between 1-5 years (174). Following treatment, there were significant reductions in blood pressure, total cholesterol, and smoking, as well as significant improvements in exercise behaviour and dietary habits. Treatment benefits were

maintained at later follow up, with the exception of smoking, and improvements in BMI had become evident(174).

3.4.4 Nervous system disorders

An increasing number of studies suggest exercise has a positive effect on cognition. For example, a systematic review and meta-analysis of RCTs in community dwelling adults older than 50 years found a 29% improvement in cognitive function for at least moderate intensity exercise. Results were independent of cognitive domain or cognitive status of participants (175). Another meta-analysis of longitudinal cohort studies of physical activity in adults ≥40 years, with prevention of cognitive decline and dementia as the focus, concluded there was a case for causality (176).

Management of stroke involves consideration of a number of major modifiable risk factors such as physical inactivity (177), high cholesterol, hypertension, metabolic syndrome, diabetes, diet and nutrition, obesity and body fat distribution (177, 178), cigarette smoking, and alcohol (177). Exercise has been shown to have a lowering effect on hypertension in several meta-analyses (179-181). Significant modification of effects on total cholesterol and LDL-C have also been observed for people with hypertension, hyperlipidemia and metabolic syndrome in another systematic review (168). Exercise also increases blood flow and improves the release of blood clot dissolving tissue plasminogen activator (t-PA). Stroke, a cardiovascular disease, has similar risk factors and requires prevention measures like those of other cardiac disorders (149, 182, 183).

3.4.5 Vascular disorders

In four systematic reviews and meta-analyses, exercise was shown to have a lowering effect on hypertension (179-181). While included studies were heterogeneous, there was a post exercise reduction in blood pressure, regardless of participant characteristics or type of exercise (aerobic and/or resistance or isometric), findings supported by the American Heart Association(184). One meta-analysis focused on isometric exercise training (179). In the other two, the lowering effect was greater when exercise was a preventive strategy in physically active participants, not taking antihypertensive medication (180, 181).

Deep vein thrombosis is particularly prevalent amongst cancer patients and an important cause of morbidity and mortality in this population (185). One systematic review reported positive effects after exercise for patients in the general population with prior or current DVT(186).

While there is no evidence for exercise in mitigating hot flashes for men receiving ADT, several studies have noted that physically active women in the general population

report fewer somatic and climacteric symptoms during menopause compared to sedentary women, suggesting that physical activity is beneficial in improving quality of life for this population (187, 188).

3.4.6 Hepatobiliary disorders

Both aerobic and resistance exercise have been shown to reduce hepatic fat content (111). Exercise impacts on fatty liver disease in a number of ways. Improved insulin resistance reduces excess delivery of free fatty acids and glucose for synthesis to the liver. In the liver, exercise increases fatty acid oxidation, decreases fatty acid synthesis, and prevents mitochondrial and hepatocellular damage (111). Two systematic reviews (189, 190) support exercise as a therapeutic strategy to improve fatty liver disease in the general population.

3.4.8 Psychiatric disorders

Depression and anxiety

A number of systematic reviews and meta-analyses have found similar effects for exercise in the general population (191) and other cancer populations (192-196). One meta-analysis of high quality exercise trials showed large and significant effects, providing robust evidence for exercise in the management of depression (191). Aerobic and mixed mode exercise were found to have large antidepressant effects across all studies when compared to no exercise controls. Supervised interventions of moderate to vigorous intensity had the largest effects and exercise supervised by professionals with relevant training such as exercise physiologists, physical educators, and physiotherapists was associated with the greatest improvements (191).

For cancer populations, several meta-analyses confirm reductions in depressive symptomology in cancer survivors following exercise interventions, mostly in those not depressed at baseline (192-196). Cancer populations included in these meta-analyses were comprised mostly of breast cancer survivors.

3.5 Exercise as medicine for men with PCa receiving ADT

Evidence for each of the CTCAE ADT adverse effect sub-groups is summarised in Table 10. The source of evidence for exercise as medicine in managing the adverse effects of ADT for PCa and brief, qualitative comments on the overall quality of currently available evidence are presented.

Table 10 Summary of evidence for exercise as medicine in managing adverse effects of ADT for PCa

Group	Adverse effect (CTCAE)	Adverse effect sub-group	Exercise as medicine evidence	Overall quality of currently available exercise as medicine evidence
1	Musculoskeletal changes	a) Bone loss	3 RCTs (135-137, 197)	** moderate evidence of significant improvements in bone loss; more exercise RCTs and more evidence of sustained improvements needed
		b) Osteoporosis	1 SR (134)	* exercise recommended but not alone; latest exercise RCT evidence not included in this medication focussed SR
		c) Fracture	0	* no evidence for falls or fractures; improved bone health & physical function may reduce risk of falls & fractures
2	Metabolic changes	a) Body composition	7 SRs (49, 139-144); 4 RCTs (135, 137, 146, 147)	***strong evidence for muscle strength and lean mass across 7 SRs & 4 RCTs; less consistent results for fat mass & waist circumference (49, 139)
		b) Metabolic syndrome	1 SR (49)	*inconclusive evidence for cardiometabolic risk markers from 1 SR
		c) Diabetes	0	*no evidence to support exercise as a management strategy
3	Cardiac disorders	a) Cardiovascular events	1 SR (153)	*little consistent evidence; emerging field suggesting improvements in cardiac and vascular function
4	Nervous system disorders	a) Cognitive impairment and dementia	0	*no conclusive evidence to support exercise as a management strategy
		b) Stroke	1 SR (153)	*little evidence, but emerging field suggesting improvements in cardiac and vascular function
5	Vascular disorders	a) Hypertension	0	*no evidence, but emerging field suggesting improvements in cardiac and vascular function
		b) Thromboembolic events	0	*no evidence to support exercise as a management strategy
		c) Hot flashes	0	*no evidence to support exercise as a management strategy
6	Hepatobiliary disorders	a) Hepatic disorders	0	*no evidence to support exercise as a management strategy
7	Reproductive system disorders	a) Gynaecomastia and breast pain	0	*no evidence to support exercise as a management strategy
		b) Sexual dysfunction	1 SR (143); 1 RCT (156)	**some inconsistency in evidence, but improved sexual function (143) & maintenance of sexual activity (156) reported for ADT PCa; more research needed
8	Psychiatric disorders	a) Depression, anxiety	5 SRs (141, 158, 159, 161, 164)	** moderate evidence for HRQoL
9	General disorders	a) Fatigue	8 SRs (49, 140, 141, 160-164); 1 RCT (165)	***strong evidence
		b) Gait disturbance	8 SRs (49, 139-142, 144, 160, 163); 2 RCTs (145, 147)	***strong evidence

Abbreviations: CTCAE Common Terminology Criteria for Adverse Events; PCa prostate cancer; ADT androgen deprivation therapy; RCT randomised controlled trial; SR systematic review; DVT deep vein thrombosis; HRQoL health related quality of life

Notes: *low level evidence; **moderate level evidence; ***high level evidence

3.6 Discussion

This rapid review has highlighted the evidence for the role of exercise in managing the adverse effects of ADT for PCa and identified where there is a lack of evidence (Table 10). There is strong evidence for exercise as medicine in addressing a number of the adverse effects of ADT such as reduced muscle mass and strength, fatigue and declining physical function. Moderate level evidence of the benefits of exercise was found for psychosocial effects of ADT (e.g. depression, anxiety, quality of life), particularly for supervised interventions; however, the evidence is not consistent across all of these effects (144). Moderate level evidence also exists for bone loss and sexual dysfunction. For the remainder of the adverse effects of ADT sub groups (osteoporosis, fracture, metabolic syndrome, diabetes, cardiovascular events, cognitive impairment and dementia, stroke, hypertension, thromboembolic events, hot flashes, hepatic disorders, gynaecomastia and breast pain), evidence is non-existent or the data to support it is limited and more research is needed to address these deficiencies.

While the exercise as medicine evidence is lacking for many ADT for PCa adverse effect sub-groups, evidence in the PCa, cancer or other clinical populations is strong and many clinical guidelines recommend exercise as a fundamental part of their clinical management (50, 51, 53, 54, 133). With the exception of gynaecomastia and breast pain, there is increasing evidence to suggest that exercise has the potential to reduce and even prevent many of the adverse effects of ADT, thus improving survivorship outcomes for men with PCa. Exercise has the potential to provide an effective approach to adverse effect management, with few associated risks. It can be combined with pharmacotherapy and/or psychotherapy where required(157), however, larger, well designed studies with longer follow-up that address more adverse effects are needed to strengthen the evidence base.

Not only is exercise effective in addressing many of the adverse effects of ADT, but epidemiological evidence for PCa drawn from prospective cohort studies, also shows a moderate inverse association between physical activity and risk of advanced and fatal disease(198). For example, outcomes from one study showed that men in the highest quintile of vigorous activity had a 77% lower risk of advanced PC(198). Men with high levels of occupational activity in another study also had lower risk of advanced PCa(198). Men with high levels of recreational physical activity in another study had a 31% lower risk of aggressive PCa than men who did not participate in recreational physical activity(198). For men already diagnosed with PCa, physical activity is associated with improved survival and decreased PCa progression(37). Vigorous activity is associated with lower risk of PCa specific mortality, both vigorous and non-

vigorous activity are associated with lower risk of all-cause mortality in this population(37). Thus, exercise is critical to health and quality of life, as well as survival, for PCa survivors.

Ideally, GPs, oncologists or urologists treating men receiving ADT for PCa would recommend exercise to manage potential adverse effects from the time of diagnosis. The ACSM advises oncologists to “Assess, Advise and Refer” so that cancer patients are connected with appropriate exercise professionals who will provide an individualised prescription(51). The prescription could take several forms but would initially incorporate assessment and a progressive program devised and supervised by an accredited exercise physiologist or physiotherapist to assist each individual to achieve improved muscle mass and strength, cardio-respiratory fitness, fat loss and body function. Depending on the capacity of the individual PCa patient or survivor, this could be accompanied or followed by a home-based program of exercise such as cycling, walking or jogging(50, 51).

While considerable evidence exists to support the use of exercise as an essential part of a cancer treatment and care plan, there has been limited uptake of this approach. Research in the UK has examined the national guidelines (NICE guidelines CG175) on exercise training for men with advanced PCa to determine whether healthcare professionals were supportive of the guidelines(57) and whether they were being implemented as part of PCa care(199). Healthcare professionals were aware of the guidelines and confused as to why no action had been taken to implement them(57). Despite the support of healthcare professionals and men on ADT, evidence-based guidelines were not being delivered. Traditional values in oncology and the need for financial support from the government to assist translation from a hospital/clinic environment were identified as the major barriers(57). A recent systematic review of interventions for PCa survivorship cautioned that more research is needed to examine the effectiveness and acceptability of exercise and psychosocial interventions outside clinical trials and to support translation into practice(144). These concerns are widely recognised. The transition to widespread application clinically and post-clinically present a challenge, particularly in design and implementation, when a targeted or personalised medical approach is viewed as critical to the efficacy and safety of exercise for cancer patients (172, 200). There is a recognised need for prescription of exercise medicine to address variation in treatment effects, treatment intensity, patient comorbidities or fitness levels(50, 172).

This rapid review is not without its limitations. While a systematic and comprehensive search was conducted, this is not a systematic review and there may be studies that were missed in the conduct of the search. In addition, qualitative judgments of currently

existing evidence were based on agreement between authors due to the heterogeneity of sources and paucity of evidence in some areas. The purpose of this review was to identify the available evidence in relation to the role of exercise in managing the adverse effects of ADT for PCa. In doing so, evidence gaps were also identified. Supplementing the evidence for the ADT PCa population with evidence from other populations supports the potential for exercise as medicine to address these evidence gaps. Future research needs to focus on the evidence gaps in relation to PCa to strengthen the current evidence base.

The use of exercise in PCa management has the potential to translate into health and economic benefits in improved quality of life and fewer complications, resulting in savings to the health care system, enhanced productivity and reduced patient and carer burden. Exercise thus has the potential to improve quality of life for this population as well as generate significant cost savings. To date, there has been no attempt to quantify the economic impact of exercise programs for men with PCa. Future research should determine the economic impact of exercise in managing the adverse effects of ADT via cost-effectiveness analysis of exercise interventions for PCa patients and survivors. Such evidence is needed to inform decision makers of the health and economic impact of exercise to support effective implementation of exercise training for PCa patients and survivors in real world settings and thus achieve research translation.

Chapter 4 Methods

4.1 Introduction

This chapter provides a general summary of the methods used to achieve the aim of this thesis which is to determine the cost-effectiveness of exercise medicine for prostate cancer (PCa). While the methods will be described in detail in each chapter, this chapter will provide a general methodological overview of the economic evaluations employed in the thesis. Although Chapter 2 established the incidence of the adverse effects of androgen deprivation therapy (ADT) and the potential impact on patients, the health system and society in terms of cost and health-related quality of life (HRQoL), the question of how best to manage these adverse effects was raised. Chapter 3 established the important role of exercise in managing many of these adverse effects. However, the cost effectiveness of exercise in managing the adverse effects of ADT for PCa is currently unknown. To date, no other studies have assessed the value for money of exercise programs to manage adverse effects of ADT for PC. Chapters 5, 6 and 7 comprise economic evaluations to determine the cost effectiveness of exercise for PCa patients and survivors treated with ADT.

The first section of this chapter (4.2) will provide a brief background to economic evaluation in health and the types of economic evaluation. The second section (4.3) will outline the approaches used in economic evaluation. The third section (4.4) situates and provides an overview of the included healthcare interventions. The final section (4.5) describes the methods employed in each economic evaluation included in this thesis (Chapters 5, 6 and 7).

4.2 Economic evaluation in health

In the 2017-2108 financial year, an estimated $185.4 billion was spent on health goods and services in Australia, accounting for over 10% of overall economic activity, with an average per capita health expenditure of $7,485(201). With increasing health care expenditure and limited resources, it is important to critically evaluate the delivery of both current and future interventions in order to ensure cost effective resource allocation. This involves comparison of opportunity cost with programme benefits, that is, the value of the benefits achievable in the original program that has been forgone in committing resources to an alternative programme(202). The aim of economic evaluation in health is to inform clinical and health system decision making and policy. Economic evaluation can be defined as “the comparative analysis of alternative courses of action in terms of both their costs and consequences”(202). All economic evaluations require the identification, measurement, valuation and comparison of the costs and consequences of the alternatives under consideration(202). The decision

question and the interventions will determine the outcomes being evaluated and the type of economic evaluation conducted(202). There are three types of commonly used full economic evaluation (those which compare alternative costs and consequences): cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA)(Table 11)(202). While cost minimisation analysis (CMA) is often included in this group of economic analyses, CMAs do not strictly conform to the definition provided of full economic evaluation. Cost minimisation analysis tends to refer to a situation where the consequences of one or more programmes or treatments are largely equivalent, such that the difference is reduced to a comparison of costs(202, 203).

Table 11 Full economic analyses

Type of economic evaluation	Measurement of consequence	Question that can be answered
Cost-effectiveness analysis	Natural units such as life-years saved, or strokes avoided	What is the cost per outcome?
Cost-utility analysis	Health state preference values (QALYs)	What is the cost of gaining the improvement in health state? How does it compare with competing interventions?
Cost-benefit analysis	Monetary units	Is this health care goal worth achieving? What is the return on investment?

Abbreviations: QALYs quality adjusted life years

A CEA is undertaken to evaluate the costs and consequences of two or more interventions where there is a single, unambiguous objective of therapy or outcome of interest(202). The incremental costs are compared with the incremental outcomes and measured in natural units. For example, diagnostic tests might be compared in terms of cost per case detected or vaccinations by cost per case prevented. The aim of CEA is to maximise health benefits while operating within a limited budget(2). While there are many advantages of using CEA such as its ease of interpretation, one disadvantage is that it cannot be used to compare interventions treating different diseases or conditions because it does not address ‘opportunity cost’. In addition, a single measure of outcome may not address the full range of patient outcomes generated by an intervention(2).

In CUA, outcomes are measured as health-related preferences (e.g. utility values), which are usually expressed as quality-adjusted life-years (QALYs) gained. The QALY attempts to capture the two most important features of a health intervention: its effect on survival in life years and its effect on quality of life. A QALY places weight on time in different health states via a utility score recorded between 1 (perfect health) and 0 (death). This is reported as the cost per QALY(204). In this way, outcomes can be compared across different disease states and used to measure opportunity cost(205). Cost-utility analysis thus addresses the comparative limitation of CEA by measuring the patient’s preference for being in a particular health state or quality of life outcome.

Because decision-makers are often required to make decisions about resource allocation across several different areas of health, the quality adjusted life year (QALY) is used as a generic measurement of outcome in CUA(2).

Both CEAs and CUAs express the incremental costs and benefits as the incremental cost-effectiveness ratio (ICER), which is the difference in cost divided by the difference in effect between mutually exclusive interventions. The term dominance is often used when interpreting ICERs. For example, one program or intervention can be said to dominate another if it is more effective and less costly. The ICER is compared with the decision maker's willingness-to-pay threshold. An intervention is said to be cost-effective when the ICER is less than the willingness-to-pay threshold. This threshold, in a budget-based healthcare system, is the opportunity cost of health benefits foregone from the investment in the new intervention(206). In Australia, a commonly used willingness-to-pay threshold is AU$50,000(207). Recently, an empirically derived reference ICER was estimated for the Australian health system suggesting opportunity costs of 1 QALY for every additional AU$28,033 of government health expenditure(208).

Another way of expressing the result of a CEA or CUA is to use the summary statistic, net monetary benefit (NMB) which represents the value of an intervention in monetary terms when a willingness-to-pay threshold for a unit of benefit is known. The NMB scales both health outcomes and use of resources to cost, permitting comparison without the use of ratios (e.g. ICERs)(209). It is calculated by multiplying the incremental benefit (ΔE) by the willingness-to-pay threshold (λ), less the incremental cost (ΔC). An intervention is cost effective when the NMB is positive ($\Delta E * \lambda - \Delta C > 0$)(210).

Cost-benefit analysis is the third type of full economic evaluation. It places monetary valuation on healthcare resources and on health outcomes, and thus provides a broader measure of value than other economic analyses(202). A CBA of a health intervention measures the monetary value of any health benefits gained by the patient, as well as the value to society of any consequences or outcomes. Welfare theory underpins the methods used in CBA. It is based on the assumption that social welfare comprises the welfare of each individual member of society and that individuals are the best judges of their own welfare. The underlying principle of welfare economics is collective willingness-to-pay or what those who gain from an intervention are willing to sacrifice to have the intervention, recognising that not all individuals will benefit and some may therefore require compensation. The focus on compensation for reduced health and willingness-to-pay for improved health led to the use of stated preference surveys to elicit willingness-to-pay for hypothetical scenarios as a way of determining

value, referred to as contingent valuation. A CBA uses these methods to assess whether the monetary value of the benefits is greater than the costs of obtaining these benefits, which is expressed as a cost-benefit ratio (total benefits divided by total costs) or return on investment (total program benefits minus total program costs)(202).

4.3 Approaches to economic evaluation

Full economic analyses, like those described above, can be conducted using patient level data from a clinical trial or using a decision-analytic model.

4.3.1 Economic evaluation of a clinical trial

Economic evaluation using trial data is conducted by measuring and averaging all relevant cost and outcome data across all patients in each trial arm to determine a mean cost and mean outcome for each patient group. The perspective of the economic evaluation will determine which resource use data from the trial follow-up is identified, measured and valued(202). This might include healthcare utilisation such as emergency department visits, hospital admissions, GP visits, and allied health appointments, as well as medications, diagnostic tests and out-of-pocket costs like travel. When conducting a CUA where the outcome measure is QALYs gained, patients complete a pre-scored HRQoL questionnaire or multi-attribute utility instrument (MAUI) (e.g. EQ-5D(211), HUI2(212), AQoL(213), or SF-6D(214), reporting their functional/health status across a variety of domains, to which the pre-existing preference weights (utility values) are attached. This health state preference data is then integrated with time to generate QALYs(215).

Costs and outcomes from the trial and the differences across the trial arms are generally presented as means (average cost and average effect), that is, when the sample size is large enough to ensure approximate normality based on the central limit theorem (CLT)(202, 216). Nonparametric bootstrapping, a technique that re-samples from a population by sampling a dataset with replacement, is also used to compare means and calculate confidence intervals. Nixon et al.(217) showed that, even with small samples from skewed data, both methods (CLT and bootstrapping) provide estimates of the mean and that bootstrapping generated at least as acceptable estimates of the uncertainty in mean values(202).

While economic evaluations based on RCTs are not guaranteed to be unbiased, prospective, trial-based analyses providing access to primary, patient level data on costs and outcomes and the opportunity to perform sub-analyses, can be beneficial both for the analysis and internal validity(202, 215). However, economic analyses are not always planned alongside RCTs and must often be conducted retrospectively, impacting on data availability and the accuracy of both costs and outcomes. For

example, the comparison therapy chosen for the trial may not be appropriate for the economic analysis if it does not provide a measure of the incremental impact of the new intervention(202). Costs incurred in a clinical trial may also need to be adjusted to reflect a real-world implementation of the intervention(202, 218).

Thus, there are disadvantages associated with relying on the results of a single clinical trial to inform decision making. It is unlikely that a single trial will compare all the interventions relevant to the disease or condition or, provide evidence on all relevant inputs and have a large enough sample to be representative of the larger population. As the purpose of a clinical trial may be to determine intermediate outcomes like improvements in cardiovascular fitness, not long term outcomes like morbidity or mortality, data is usually collected for a short period of time, with no indication of the longer term implications for health outcomes and costs(202, 219). Data for the trial population may not be representative of other populations within or outside the country and thus may not be relevant to the decision context. Relying on a single trial may also mean evidence from other trials or sources, such as observational studies or meta-analyses, is excluded and does not support an economic evaluation of the rigour required to inform regulatory or policy decisions. It is not uncommon, therefore, for retrospective economic analyses to utilise multiple trials or sources of information in the construction of a model(219). Decision-analytic models based on trial data and evidence synthesis is thus the preferred approach to economic evaluation for the purpose of informing decision making.

4.3.2 Economic evaluation using decision analytic models

Frameworks such as decision-analytical modelling provides a feasible alternative to clinical trials. Modelling uses secondary or derived data on efficacy, health state transitions and utilities for the development of the model from a single clinical trial, multiple trials or a combination of sources (clinical data, meta-analysis, the literature). Modelling thus provides a way of bringing evidence from a diverse range of sources together to address uncertainty(219).

The first stage in developing a decision model is to specify the decision problem or clearly identify the question to be addressed in the analysis, based on the requirements of the decision maker(219). Then the scope or boundaries of the evaluation need to be established by identifying the perspective, the populations expected to benefit, the location and the setting, the treatment or intervention options, the time frame and the outcome measures(219, 220).

The second stage is to develop the model structure. Commonly used models include decision trees, Markov models, micro-simulation, discrete event simulation and

dynamic models(221). A general rule of thumb is to use the simplest model that fits the purpose(222). The decision tree is the simplest form of a decision model and is typically adequate for simple problems with short time frames. However, when the decision problem involves a number of health states, a Markov model is more equipped to handle the complexity of modelling options with numerous possible consequences(219). Rather than modelling possible consequences over time using a large number of possible pathways as in a decision tree, Markov models are structured around mutually exclusive disease (health) states reflected as a set of possible transitions between the disease (health) states, over a series of discrete time periods or cycles(219). Where individual considerations, such as patient history are important, patient level simulation is a more appropriate modelling framework or when the treatment process involves interactions between individuals, discrete event simulation would better capture the effects of these interactions. A combination of different model types may also be appropriate for some decision problems. Regardless of the model framework chosen, all structural assumptions such as cycle length and time horizon should be adequately described and justified(219, 221).

The third stage is to identify and synthesize the evidence for the input parameters of the model(219). Data inputs used to populate the model should be derived from the best available sources of evidence. When the evidence required for all variables has been collected, the model can be run for each intervention to estimate the costs and outcomes. Results are typically presented as ICERs and NMBs(219).

The model provides a framework for synthesising the available evidence from a range of sources together to estimate costs and outcomes for the intervention and determine the cost-effective option, rather than relying on a single RCT. Decision rules can be applied to determine the optimal alternative based on the evidence. Models can thus provide flexibility to incorporate heterogeneity and identify uncertainty and future research priorities. The results are, however, dependent on the availability of data and the assumptions that underlie or form the structure of the model(219, 223). Modelling, therefore, is important, particularly when there are resource allocation decisions to be made, providing that the methods employed are sound and critically reviewed. When faced with conducting an economic analysis, the economist must decide to use the clinical data as collected, supplement it, adjust it to reflect a more naturalistic setting or incorporate modelling.

Uncertainty is inherent in every economic evaluation to some degree and can arise from methodological assumptions, the data used in the analysis, the need to extrapolate data over time or generalize results to other settings. Methods for handling uncertainty vary according to the source of the uncertainty and the type of economic

evaluation(202). For example, if the economic evaluation involves a patient level analysis with stochastic data, uncertainty in the form of sampling variation can be addressed using statistical analysis, extrapolation using modelling methods and generalisability using sensitivity analysis. In decision-analytic modelling studies, the preferred method for parameter uncertainty is probabilistic sensitivity analysis and for modelling uncertainty and generalisability, sensitivity analysis. For both types of economic evaluation, patient level analysis or decision analytic modelling, methodological uncertainty is best addressed via sensitivity analysis or methodological standards, such as a 'reference case'(202).

4.4 The healthcare interventions

The Exercise Medicine Research Institute (EMRI) was established in 2003 and houses a productive, multidisciplinary exercise science research team, dedicated to investigating the extent to which exercise can be employed in chronic disease management, principally cancer, to improve patient outcomes. Central to the Institute's achievements in cancer research is the unique combination of clinical patient care, exercise medicine, and innovation in health interventions. Their seminal work in PCa has enabled translation of their research findings into practical outcomes for patient benefit and led to the design and implementation of clinical and community-based cancer survivorship programs(224). Researchers from EMRI are part of the research team at the Centre for Research Excellence in Prostate Cancer Survivorship, which received funding from the National Health and Medical Research Council (NHMRC) in 2016(225).

Exercise interventions for men receiving ADT for PCa have been shown to be effective at managing many of the associated adverse effects (Chapter 3), yet no economic evaluations have been conducted to determine the cost-effectiveness of these interventions. As PCa involves a number of stages, and the needs of men at various stages are different, it is important to include exercise interventions that address these differences. For this reason, economic evaluations were conducted of two clinical trials. These clinical trials provide a platform from which to begin exploration of the cost-effectiveness of supervised exercise for men receiving ADT for PCa. The first trial was a small RCT of supervised exercise for men receiving ADT for advanced disease, metastatic to bone(34). This population are often excluded from exercise RCTs due to fear of fragility fracture and thus, also difficult to recruit. Given the high risk of falls and fractures and elevated mortality risks after a fall in this population, it is particularly important to establish the safety and efficacy of supervised exercise. The results of this RCT showed that supervised exercise was safe for PCa

patients with bone metastases. At 3-month follow-up, there were significant differences favouring the exercise group in physical function (greater strength in leg extension, and faster speeds over the 400m and 6m timed walks), improved physical activity and body composition (increases in whole body and appendicular lean mass)(34).

The second RCT involved men with a longer life expectancy, who were from the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial(36). Long-term PCa survivors are at increased risk for comorbidities and physical deconditioning, so the aim of this trial was to determine the effectiveness of a year-long randomised controlled trial of exercise training on physical functioning in PCa survivors more than five years after diagnosis. The sample size in this trial was larger (n=100) and the follow-up longer (6-months supervised + 6-months home-based exercise). For those in the intervention group, results showed significant improvements in cardiorespiratory fitness, lower body physical function and muscle strength, as well as increases in appendicular lean mass(36).

Given the limitations associated with economic evaluations of single clinical trials described above, a decision-analytic framework using Markov modelling was employed for the third economic evaluation, a cost-utility analysis of exercise for men with high risk localised or locally advanced PCa receiving curative therapy and ADT. The methods employed in these three economic evaluations are briefly described below.

4.5 Economic evaluation of the healthcare interventions

4.5.1 Cost-effectiveness analysis of a pilot RCT of supervised exercise for PCa patients with bone metastases (Chapter 5)

A trial-based economic evaluation of the above RCT, a pilot, 3-month supervised exercise intervention versus a recommendation to exercise is conducted. An Australian healthcare payer perspective is presented as a reference case analysis with a societal perspective presented as a sensitivity analysis. The primary outcome measure for the economic analysis is QALYs, estimated by the area-under-the curve method from patient-reported health status at baseline and three months using the SF-36 questionnaire(226). QALYs are calculated from participant responses using the SF-6D standard gamble health state valuation to estimate utility, a preference based single index score(227). UK weights based on Brazier et al. were used to value the SF-6D because the original analysis was conducted in 2014 before the release of the Australian utility weights(214). QALYs were generated by multiplying three months of life by the utility score for each participant.

Costs and monetary benefits are expressed in Australian dollars (AUD) at 2018 prices. Costs and effects are not discounted because the duration of the trial is one

year. Random sampling of the intervention and control group (n=20) is conducted to generate values for the non-parametric bootstrapping used to derive uncertainty intervals around point estimates of the ICERs. Bootstrapping with replacement is used to generate 1000 cost and outcome pairs to determine the probability distribution of costs and outcomes, which are plotted on a cost-effectiveness plane. Cost-effectiveness acceptability curves are derived to depict the probability that the intervention is cost effective across a range of willingness-to-pay thresholds.

Given the high levels of uncertainty associated with a pilot study with a small sample size, a value of Information (VOI) analysis is conducted. VOI is a systematic approach to measure decision uncertainty and determine whether there is sufficient evidence to support the adoption of new interventions(228). It provides a framework for quantitatively estimating the value of additional evidence in informing a decision. By estimating the probability of error and the opportunity costs of error, the expected cost of uncertainty or expected opportunity loss associated with a decision can be calculated(219). This involves the difference between the expected net benefit of a decision made without perfect information (current information) and one made with perfect information. This is referred to as the expected value of perfect information (EVPI) and, because decisions are taken at the population level, population EVPI is also calculated(219, 229).

4.5.2 Cost-effectiveness analysis of a supervised exercise intervention for men with PCa previously treated with radiation therapy and androgen deprivation therapy (Chapter 6)

A trial-based economic evaluation of the above RCT, a six-month supervised exercise intervention versus a recommendation to exercise and a physical activity booklet is conducted. An Australian healthcare payer perspective is presented as a reference case analysis with a societal perspective presented as a sensitivity analysis. The primary outcome measure is QALYs gained which are calculated from participant responses to the SF-36 questionnaire using the SF-6D standard gamble health state valuation to estimate utility, a preference based single index measure for health(226, 227). QALYs are generated by multiplying six months of life (the follow-up period for the supervised intervention) by the utility score for each participant. Costs and monetary benefits are expressed in Australian dollars (AUD) at 2018 prices. Costs and effects are not discounted because the duration of the trial is one year. Random sampling of the intervention and control group (n=100) is conducted to generate values for the non-parametric bootstrapping used to derive uncertainty intervals around point estimates of the ICERs. To determine the probability distribution of costs and outcomes, 1000 cost and outcome pairs are generated by bootstrapping with

replacement and plotted on a cost-effectiveness plane. Cost-effectiveness acceptability curves are derived to depict the probability that the intervention is cost effective across a range of willingness-to-pay thresholds.

4.5.3 Cost-utility of a supervised exercise intervention to prevent falls and fractures in men with PCa: a Markov model (Chapter 7)

Limitations of within trial analysis and advantages of a modelled analysis are described above (4.3.2). A decision-analytic framework using Markov modelling is conducted for the third economic evaluation, a cost-utility analysis of exercise for men with high risk localised or locally advanced PCa receiving curative therapy and ADT. The analysis is conducted from an Australian healthcare payer perspective. The time horizon is three years so as to capture the longer-term impact of ADT on physical function and bone mineral density, which can impact on risk of falls and fractures. Costs and monetary benefits are discounted at 5% over the time horizon and expressed in Australian dollars at 2019 prices. The primary outcome measure is NMB. This model incorporates evidence from the literature, outcomes from clinical trials and expert knowledge. All economic evaluations included in this thesis conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement(230), and the ISPOR Good Research Practice Guidelines for Cost-effectiveness Analysis Alongside Clinical Trials(231).

Chapter 5 Demonstrating the value of early economic evaluation alongside clinical trials: exercise medicine for men with metastatic prostate cancer

5.1 Introduction

Prostate cancer (PCa) patients with bone metastases tend to have significant functional impairment from long-term androgen deprivation therapy (ADT), exacerbated by subsequent treatments such as second-line hormone therapies (abiraterone and enzalutamide), first and second line chemotherapy or immunotherapies(56). They are at significant risk of falls, fractures and consequent hospitalisation. There is a growing body of evidence to support the effectiveness of exercise in addressing the adverse effects of advanced PCa treatment(50). Despite recommendations for men with bone metastases to participate in supervised exercise, there is often a reticence on the part of clinicians and/or patients due to concerns of fragility fracture or other adverse effects(56). These men with significant treatment toxicity and a high disease burden are an important patient group for whom exercise has been demonstrated to improve quality of life (QoL)(147). To inform policy and improve accessibility of exercise for advanced PCa patients, it is important to determine whether such interventions represent value for money.

Economic evaluations of effective programs, especially those based on the outcomes of randomised controlled trials (RCTs), are important sources of information to support decision-making about allocation of scarce resources. To date, no cost-effective analyses (CEAs) of exercise interventions for PCa patients with bone metastases have been conducted. Therefore, in this article, we demonstrate how an exploratory CEA of a pilot RCT of supervised exercise training for men with metastatic PCa can determine whether this exercise intervention is potentially cost-effective compared to usual care and, using value of information (VOI) analysis, whether a larger RCT is worthwhile.

5.2 Cost-effectiveness analysis methods

A trial-based CEA was conducted of a pilot RCT involving 20 patients with metastatic PCa at university affiliated exercise clinics in Perth, Western Australia, from July 2011 to July 2012(34). Ten patients were randomised into each arm: resistance exercise or usual care. There were no significant differences between groups at baseline. The exercise intervention involved twice-weekly 60-minute resistance exercise sessions conducted in small groups over 12 weeks. Usual care involved maintaining customary activities throughout the intervention period. Outcome assessments were conducted at baseline and after the 12-week intervention and

included objectively measured and patient-reported outcomes. Details of the study methods and outcomes are reported elsewhere(34).

The CEA was conducted from a healthcare payer perspective. The primary outcome measure was quality adjusted life years (QALYs), calculated by multiplying the utility weight by the duration spent in each health state from patient-reported health status at baseline and after the 3-month intervention using the SF-36 questionnaire. Participant responses were scored using the SF-6D standard gamble health state valuation to estimate utility weights, a preference based single index score measured on a cardinal scale which typically ranges from 0 (death) to 1 (best health). The duration in each health state was then multiplied by the utility weight to calculate QALYs(227).

Costs associated with the intervention were calculated as those costs additional to usual care of PCa patients. The total cost of implementing the exercise intervention included labour costs for participant registration, a pre-intervention consultation with an accredited exercise physiologist (AEP), administration and conduct of exercise sessions by the AEP, and the GP visit to determine eligibility to participate in exercise training.

We compared mean costs and mean effects between the intervention and control groups to determine incremental cost and incremental effect. Incremental cost-effectiveness ratios (ICERS) were calculated, which represent the additional expenditure required to deliver each additional unit of benefit. We set WTP at $AU50,000 per QALY, a commonly used threshold for cost-effectiveness in Australia(207).

To derive uncertainty intervals around point estimates of the ICERs, non-parametric bootstrapping was used by random sampling of values from the intervention and control groups (n=20). The economic analysis was carried out using Excel for Office 365 (MSO 2016, Version 1902, Microsoft, Seattle). All costs were reported in Australian dollars (AU$) and adjusted to real prices in the 2018 reference year(232) (AU$1 ≈ £0.56; US$ 0.68). Discounting future costs and benefits was not used due to the 12-month trial duration.

5.3 Value of information analysis methods

To estimate the potential value for money of future research (e.g. larger RCT), VOI analysis was conducted. VOI provides a framework for quantitatively estimating the value of additional evidence to reduce uncertainty and better inform funding decisions. It considers the probability of a funding decision error, the opportunity costs of error, and the size of the population expected to benefit from research results over a given

time horizon(228). Based on the bootstrap simulation, we calculated the expected value of perfect information (EVPI), which is the difference between the expected monetary benefit of a decision made without perfect information (current information) and one made with perfect information. The estimated EVPI was scaled up to the population expected to benefit from the intervention (i.e., men with metastatic PCa) over the coming 10 years with a 5% discount rate(228). To calculate population EVPI, the 2017 PCa prevalence was converted to absolute incidence and projected to 2028 (233, 234). Men with metastatic cancer in Australia represent approximately 3% of this population (n=13,122)(233).

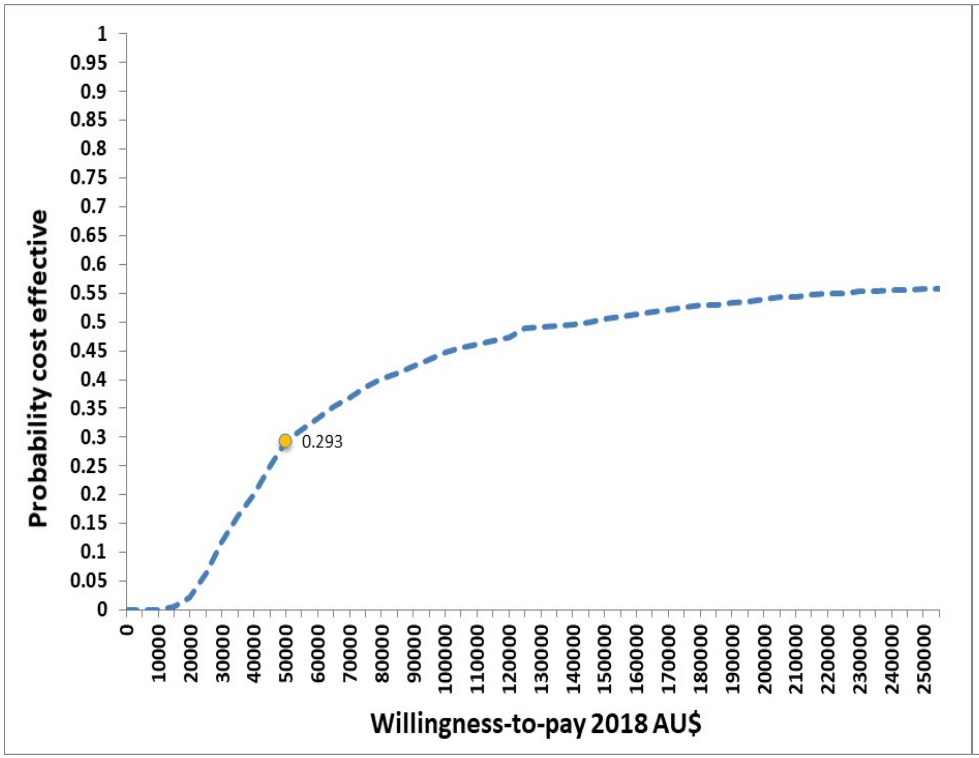
5.4 Results

Cost-effectiveness results for the three months of the pilot study are shown in Table 12. The intervention group cost $461 more than the control group per patient. The QALY gain for the intervention group versus the usual care group was 0.0035, with an incremental cost per QALY gained of $133,509. A cost-effectiveness acceptability curve of gains in QALYs shows that, at a WTP of $50,000, the base case intervention would have a 30% probability of being cost-effective (Figure 3a); the probability distribution of costs and outcomes, generated by bootstrap sampling, are depicted on the cost-effectiveness plane (Figure 3b).

Table 12 Cost-effectiveness results for supervised exercise intervention

Variable	Control group	Intervention group	Difference (95% CI)	ICER (95% CI)
Mean cost	$0	$461	$461	
Mean QALYs	0.1741	0.1776	0.0035 (-0.0162 - 0.0225)	$133,509 ($20,494 - Dominated[1])

Abbreviations: ICER incremental cost effectiveness ratio; QALY quality adjusted life years
Notes: [1]Fewer QALYs gained at an additional cost



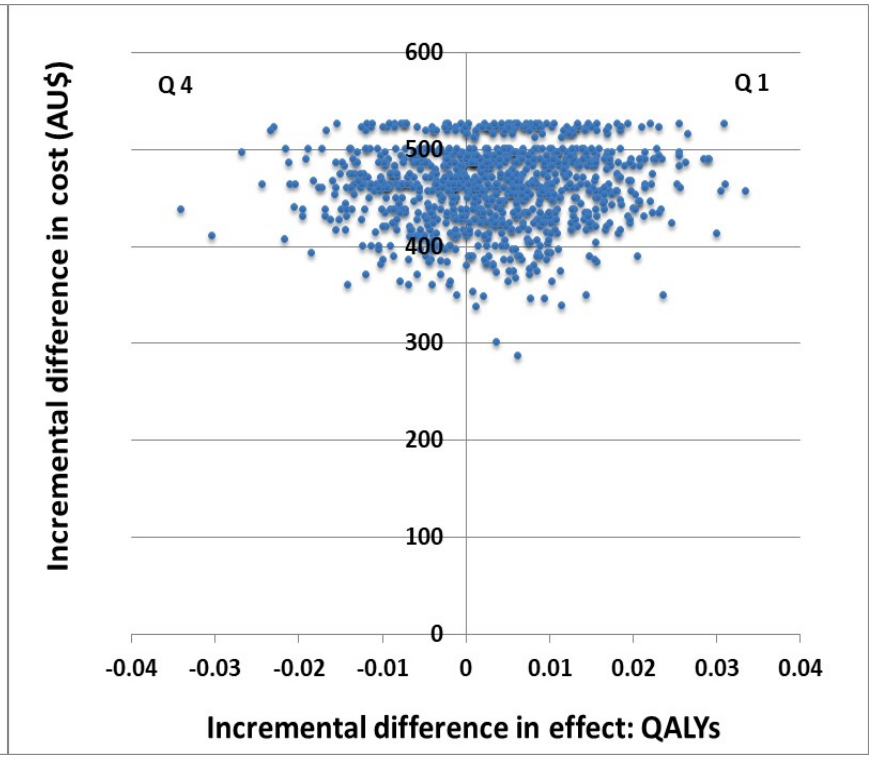


Figure 3 Cost-effectiveness results: QALYs (3a & 3b)

Figure 3a **Cost-effectiveness acceptability curve showing probability supervised exercise intervention was cost-effective compared to usual care**

● Willingness-to-pay threshold AU$50,000

Figure 3b Bootstrap results on the cost-effectiveness plane: incremental costs and incremental QALYs

Q1: quadrant 1 more effective and more costly than comparator

Q4: quadrant 4 less effective and more costly than comparator

The per person EVPI for the intervention group was $85. The population EVPI for the intervention was $971,520 which represents the upper-bound (i.e., maximum) expected benefit of future research. While there are opportunity costs to funding any research, if the population EVPI exceeds the expected costs of additional research (direct research costs and indirect (i.e. opportunity cost), then additional research is potentially worthwhile (i.e., it is likely to be cost-effective to conduct further research).

5.5 Discussion

This study investigated approaches to economic analysis of exercise interventions for PCa patients with bone metastases to examine the potential value of a larger trial. The intervention achieved a small QoL gain and was effective in increasing physical activity, improving physical function and increasing lean body mass, thus addressing a number of the risks confronted by PCa patients with bone metastases. However, the costs to gain these QoL and clinical benefits were relatively expensive.

The main limitation of the analysis was the small sample size of the pilot study, the consequence of an older population with high disease load, typically difficult to enrol in exercise trials(34). In addition, no data were collected beyond three months, which meant that it was not possible to determine post intervention outcomes such as falls, fractures, adverse events, metabolic and lifestyle diseases or further improvement in trial outcomes for participants. The absence of such data means that related healthcare treatment costs or cost-savings for the post intervention phase could not be captured, which would have an impact on the CEA.

Due to the uncertainty associated with a small sample, short follow-up and lack of evidence required to construct a modelled analysis of the impact of exercise on the adverse effects of ADT for PCa patients with bone metastases, the feasibility of more research to enhance decision making is an important consideration. VOI analysis generated a population EVPI of $971,520 over ten years, suggesting a further study, undertaken for a lower cost than the EVPI, is likely to be worthwhile.

To improve the quality of economic evaluations conducted alongside clinical trials, there is a need for these evaluations to be part of early pilot studies to demonstrate feasibility and inform economic data collection in future studies. Under constrained research resources (e.g. funding and participants) quantitative approaches such as VOI analyses can be applied to inform the value for money of larger RCTs. Early economic evaluations are important in identifying research gaps in order to more rapidly advance an important field of study such as exercise for PCa patients with bone metastases. Future research should address the methodology to better capture health benefits and involve a larger sample with longer follow up to improve CEA in this

population. Improved CEA means better informed decision makers, and potentially, more accessible exercise and improved QoL for PCa patients with bone metastases.

Chapter 6 Cost-effectiveness analysis of supervised exercise training in men with prostate cancer previously treated with radiation therapy and androgen deprivation therapy

6.1 Introduction

Prostate cancer (PCa) is a significant public health issue. It has a high incidence and is the cause of significant morbidity and mortality. In Australian men, it is the most commonly diagnosed cancer and the second most common cause of cancer death after lung cancer(234). PCa needs testosterone, an androgen (male sex hormone), to grow. Androgen deprivation therapy (ADT), which reduces or blocks androgen production, is thus widely used across the spectrum of PCa from high-risk localised disease to metastatic disease. However, it is associated with potentially debilitating adverse effects such as changes in body composition (e.g., increased fat mass, reduced muscle mass [sarcopenia]), metabolic complications and decline in physical function. The risk of adverse effects is an important consideration for men with long life expectancies, such as those men receiving neoadjuvant or adjuvant therapy with curative radiation(36). In older PCa survivors (>70 years), testosterone does not always recover, so adverse effects for this population may not be temporary(36).

Exercise has been shown to be effective in addressing metabolic function and associated comorbidities (e.g. diabetes, CVD, etc.), as well as sarcopenia and significant functional impairment resulting from long term androgen deprivation(36, 48, 49, 139, 141, 142, 161, 199, 235-237). A recent meta-analysis of exercise for cancer randomised controlled trials (RCTs) using individual patient-level data found that supervised exercise effectively improves quality of life and physical function across sub groups of cancer patients with different demographic and clinical characteristics, both during and after treatment(235). In addition, an umbrella systematic review of meta-analyses of exercise clinical trials concluded that exercise was beneficial for cancer survivors, and seventy-five per cent of these beneficial effects were statistically significant(236). The largest effect sizes were for cardiovascular fitness and muscle strength. If increased physical activity significantly improves cardiorespiratory fitness, muscle mass and physical functioning, which can potentially reduce the risk of metabolic diseases and comorbidities, as well as falls and subsequent fractures, and improve quality of life, then it is important to determine whether such interventions are cost effective to implement.

Economic evaluations of effective programs, particularly those based on the outcomes of RCTs, play an important role in the allocation of scarce resources. Cost-effectiveness analysis evaluates the effectiveness of interventions relative to their cost with the purpose of informing health care policy decision making(202). While there has

been an increase in the number of studies evaluating the cost- effectiveness of exercise interventions in recent years, only a small number of studies have investigated the impact of exercise interventions on adults with cancer(238-245). Eight studies were identified in the literature, six related to breast cancer(239, 241-245), one to lung cancer(238) and another to a number of different cancers (breast, colon, ovarian, cervical, testicular and lymphoma)(240). Mode of delivery of exercise interventions differed across studies, from the use of a DVD in the home with no supervision(239); delivery by physiotherapists(240-243, 245); or face-to-face or telephone delivery by qualified exercise physiologists (AEPs) (244, 245). Intensive exercise interventions for cancer patients were most often not cost effective. Results of the economic analyses tended to generate high incremental costs per QALY and/or low probability of cost-effectiveness, and none included participants with PCa. Given that over 80% of Australian men diagnosed with PCa have Stage I or II disease, they will potentially need to manage the impacts of ADT for a long period of time(234). Therefore, identifying those most likely to benefit from increased physical activity, and the cost and cost-effectiveness of providing exercise interventions is important, and especially important for those with PCa receiving ADT.

We conducted an economic evaluation of a multi-centre RCT of supervised exercise training (resistance and aerobic) in long-term PCa survivors (>5 years post diagnosis) from the Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial designed to determine the effectiveness of supervised exercise training on cardiovascular fitness and physical functioning(36).

6.2 Methods

6.2.1 RCT targeted population, setting and location

A multicentre, RCT of exercise training (resistance and aerobic) was conducted with long-term PCa survivors previously treated with ADT and radiotherapy from the TROG 03.04 RADAR trial. One hundred PCa survivors diagnosed approximately five years previously were randomised into one of two arms: 1. a 6-month supervised exercise intervention followed by a 6-month home-based maintenance programme or 2. a general recommendation to perform 150 minutes of moderate physical activity based on a printed booklet. Supervised exercise comprised twice weekly 1-hour sessions in small groups for six months and consisted of moderate- to high-intensity resistance training using exercise machines and aerobic exercise such as walking, cycling or jogging. The exercise intervention was supervised by accredited exercise physiologists in 13 university-affiliated exercise clinics across Western Australia, New

South Wales and Wellington, New Zealand(36). The comparator arm represents usual care; healthcare providers should recommend their patients perform 150 minutes of moderate physical exercise per week(50, 51).

There were no significant differences in characteristics between the two groups(36). For the total sample, baseline means were as follows: age - 72 years; time since radiation cessation - 51 months; time since ADT cessation - 38 months; and duration of previous ADT - 12 months. Outcome assessments were conducted at baseline, after the initial 6-month supervised exercise portion of the intervention and at 12 months after the 6-month home-based maintenance program. Details of the study methods are reported elsewhere, as well as intervention effects at six months(36). The RCT was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000729224) and approved by the Edith Cowan University Human Research Ethics Committee (HREC No. 3636).

6.2.2 RCT outcomes

The primary trial outcome (400 metre walk test) at 6-month follow-up significantly favoured the intervention group. The adjusted mean group difference in cardiorespiratory performance between groups for the 400 metre walk test was 19 seconds (95% CI 3.95 - 42.0; p=0.029)(36).

6.2.3 Economic evaluation

A trial-based economic evaluation of the 6-month supervised exercise portion of the RCT versus a recommendation to exercise and provision of a physical activity booklet was conducted. The 6-month intervention included 100 men aged 62-85 years, 50 in each arm(36). The 12-month SF-36 outcome data collected after the home-based maintenance exercise program was not incorporated in the main analysis because the initial intention was to capture the benefits of supervised exercise. Exercise intervention adherence and sustainability is a recognized problem in exercise interventions for older community dwelling adults(246). At-risk and frail older adult populations tend not to maintain behavioural change or functional improvement at 12 months post intervention(247), however, for this trial, there is evidence of benefit maintenance post intervention. In addition, older adults who are physically active have been shown to maintain behavioural and functional improvement from 6-24 months post intervention(247-250). With consideration of this evidence and the fact that the intervention involves men with PCa, for whom little evidence currently exists outside this trial, maintenance of HRQoL outcomes at 12 months are presented as a sensitivity analysis.

An Australian healthcare payer perspective was presented as a reference case analysis with a societal perspective presented as a sensitivity analysis. This paper conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement(230), and the ISPOR Good Research Practice Guidelines for Cost-effectiveness Analysis Alongside Clinical Trials(231).

6.2.3.1 Primary outcome: Quality adjusted life years (QALYs)

The primary outcome measure for the economic analysis was QALYs, estimated by the area-under-the curve method from patient-reported health status at baseline and 6 months using the SF-36 questionnaire, a measure of general health widely used in clinical studies internationally(226). QALYs were calculated from participant responses using the SF-6D standard gamble health state valuation, a preference based single index measure for health, to estimate utility(227). UK weights based on Brazier et al. were used(214). QALYs were generated by multiplying six months of life (the follow-up period for the supervised portion of the study) by the utility score for each participant.

6.2.3.2 Secondary outcome: Cardiorespiratory fitness and functional mobility

Cardiorespiratory fitness is important in addressing metabolic and CVD risk, as well as risk of falls and fractures, particularly for men who have received curative treatment and ADT for PCa, who typically have a relatively long life expectancy. The 400-metre walk, measured in seconds, was the secondary outcome for the economic analysis. Performance on this test is associated with mortality, CVD and functional mobility(251, 252).

6.2.3.3 Measuring resource use and costs

The total cost of implementing the physical activity intervention was estimated from a healthcare payer perspective. Costs arising from research (e.g. cost of heart monitor for exercise arm and pedometers for both arms of the trial) and development (engagement with oncologists and general practitioners (GPs) to refer patients; time spent on development of exercise booklet for control arm) were excluded so that only the costs of replicating the intervention were captured. Project records relating to intervention delivery, including costs, were kept for the period of the trial. Implementation costs included labour for participant registration, a pre-intervention consultation with an accredited exercise physiologist (AEP), administration and conduct of the exercise sessions by the AEP, and the GP visit to determine eligibility for inclusion in the trial. Resource use costs included those costs specific to the intervention such as communication (telephone calls) with participants, material and printing costs.

A societal perspective was estimated as a sensitivity analysis (see SA2 below)(253). Participant out-of-pocket costs for the sensitivity analysis (SA2) included gym membership as a proxy for attendance at the university exercise clinic (imputed as an average concession rate across a number of gyms) and travel costs for the six months participation. It was assumed that participants would choose a gym that was relatively close and convenient to their home or workplace, hence minimising travel time and cost.

6.2.3.4 Valuing resource costs

To provide monetary values for resource use, prices or unit costs were applied. Resources were valued using local or national costs where appropriate. All costs were reported in Australian dollars (AU$) (AU$1 ≈ US$ 0.68) and adjusted to real prices in the 2018 reference year(232). Discounting was not applied due to the evaluated portion of the trial being less than 12 months. Usual care involved an information booklet on exercise and a recommendation to exercise for 150 minutes per week, so the cost assigned to usual care was that of the information booklet. The incremental costs associated with the intervention were calculated as those costs additional to usual care of PCa survivors. Edith Cowan University (ECU) higher education worker (HEW) pay scales were used to impute labour costs for graduate AEPs(254). On-costs (labour costs in addition to salaries and wages such as superannuation, payroll tax, workers compensation and long service leave) of 30% were included. This figure was used to account for variation arising from casual, short-term or ongoing contractual arrangements (16%-40%)(255). Attendance was collected for twice weekly exercise sessions and this cost was based on attendance of four people per session across 13 gyms for the period of the trial. The cost of the Level B GP visit was determined using the Australian Medicare Benefits Schedule (MBS)(256). All other resource use categories were valued using market rates.

For the societal perspective, patient out of pocket exercise session costs were imputed as concession rate gym membership averaged across a number of exercise facilities. Travel costs were estimated based on a cents per kilometre rate (AU$0.64) for a car with a 1600cc engine, as per the Australian Taxation Office(257). Distances travelled were estimated from participant data collected by exercise physiologists. In calculating a representative travel cost, consideration was given to participants using public transport(258).

6.2.3.5 Cost-effectiveness analysis

Cost-effectiveness analysis was carried out using Microsoft® Excel version 16.0.1 (Microsoft, Seattle). We compared the mean costs and mean effects between the

intervention and control groups to determine incremental cost and incremental effect. Missing data for the primary outcome measure (QALYs) was addressed using maximum likelihood imputation (expectation maximisation). SF-36 generates multiple values within eight domains. From these values a composite utility score using the SF-6D algorithm is calculated. However, missing values in any of the eight domains results in the utility values not being generated. For the purposes of calculating accurate utility values and QALYs gained for the economic analysis, multiple imputation was conducted separately for the SF-36 baseline and six-and 12-month outcomes in R (version 3.4.1 (2017-06-30) – "Single Candle"). In order to check for convergence, five imputations (with 30 iterations each) using multiple imputation by chained equations (MICE) was computed. Predictive mean matching (imputations are restricted to the observed values) was used to impute the variables of interest(259). In addition, the iNMB was calculated as the difference in mean QALYs multiplied by the maximum willingness-to-pay for a QALY minus the difference in mean cost.

Incremental cost-effectiveness ratios (ICERs) were calculated for the secondary outcome (cardiorespiratory fitness and functional mobility) and represent the additional expenditure required to deliver each additional unit of benefit. The ICER calculated was the cost per mean reduction in walking time (seconds) over 400 metres. The difference in mean costs was divided by the difference in mean effects between the intervention and control groups over the six months of the intervention.

6.2.3.6 Uncertainty analyses

Random sampling of the intervention and control group (n=100) was conducted to generate values for the non-parametric bootstrapping used to derive uncertainty intervals around point estimates of the ICERs. To determine the probability distribution of costs and outcomes, 1000 cost and outcome pairs were generated by bootstrapping with replacement and these were plotted on a cost-effectiveness plane. Cost-effectiveness acceptability curves were derived to depict the probability that the intervention is cost effective given a decision maker’s willingness-to-pay per QALY.

6.2.3.7 Sensitivity and scenario analyses

Univariate sensitivity analyses were undertaken to explore the impact on the ICER of variations in the evaluation components from the trial (Appendix 4). These included: Sensitivity analysis 1 (SA1). variation in the magnitude of effect size using the upper and lower confidence interval limits; Sensitivity analysis 2 (SA2). societal perspective based on addition of patient out-of-pocket costs; Sensitivity analysis 3 (SA3). variation in cost based on number of participants attending the exercise session and reduced pre-consult time with AEP; and Sensitivity analysis 4 (SA4). maintenance of quality of

life outcomes after the 6-month home-based exercise program. Two scenario analyses were also undertaken to explore their potential cost-effectiveness. Scenario 1 (S1) involved scaling up the intervention to a community-based group based on a minimum of 10 participants, MBS costs for the AEP, and administrative staff wages to reduce implementation costs. Scenario 2 (S2) involved a private cancer clinic in-house exercise gym. The provision of the gym is part of the business model as a way of creating competitive advantage. Patient requires a Chronic Disease Management Plan and cost of exercise equipment and maintenance is included as an opportunity cost in patient fees.

6.3 Results

6.3.1 Costs and outcomes

Intervention costs calculated are shown in Table 13 From a healthcare payer perspective, the cost of the intervention over six months was calculated as AU$550 (2018). The cost of the control arm, usual care, was AU$4 (2018) for the provided exercise booklet, because usual care for PCa survivors is typically a recommendation to do light to moderate exercise or no advice, creating no additional cost. The incremental cost of the intervention was thus AU$546 (2018).

Table 13 Breakdown of costs of exercise intervention over 6 months of RCT

Intervention cost component	**Cost description**	**Unit of measure**	**Cost per participant AU$**
GP consent	MBS Item 23: Level B GP consultation less than 20 minutes	1 consultation ($37.05)	$37
Registration of RCT participants	ECU HEW level 5 Step 2 + 30% on-costs $78,335 (2012)	1.3% of workload allocated across 2 concurrent programs	$20
Program administration	Calls to participants during intervention	Three calls per participant at 0.26	$1
AEP pre-program consultation	1 hour consult @ HEW level 5 Step 2 + 30% on-costs	Hourly rate ($30.38) + 30% on- costs	$40
Subtotal			$98
26-week exercise intervention	1 hour consult @ HEW level 5 step 2 + 30% on-costs mean no. of sessions attended 40	4 participants (mean no.) per session over 6 months follow up of trial across 13 gyms Hourly rate $40.17	$402
Total healthcare perspective (rounded to nearest 2011$)			$500
Adjusted to 2018$			**$550**
Societal perspective: Participant out of pocket costs			
Exercise program membership	6-month concession exercise membership averaged across several exercise clinics	6 months while participating in intervention; approx. $25/fortnight	$325
Travel	Car costs/return bus travel mean no. of sessions (n=40)	$0.64 per km 1600cc engine. Approx. $5/week or $2.50/ session attended (includes consideration of those who take free public transport)	$100
Total societal perspective (rounded to nearest 2011$)			**$925**
Adjusted to 2018$			**$1017**

Abbreviations: GP general practitioner; MBS Medicare benefits schedule; RCT randomised controlled trial; ECU Edith Cowan University; HEW higher education worker; AEP accredited exercise physiologist.

6.3.2 Outcomes

The results for the primary and secondary outcomes are reported in Table 14.

Table 14 Cost-effectiveness results for supervised exercise intervention

Variable	Control group	Intervention group	Difference (95% CI)	ICER (95% CI)
Mean cost	$4	$550	$546	
Mean QALYs	0.3681	0.3766	0.0085 (-0.0093 - 0.0256)	$64,235 ($21,307 - Dominated[1])
Mean seconds change in walking time (400m walk test)	2.9	-18.6	19[2] (3.95 - 42.0)	$29 ($13 - $110)

Abbreviations: ICER incremental cost-effectiveness ratio QALYs quality adjusted life years
Notes: [1]Fewer QALYs gained at an additional cost; [2]adjusted for baseline

Quality adjusted life years gained for the intervention versus the usual care group was 0.0085, with the incremental cost per QALY gain at six months being AU$64,235. At a willingness-to-pay of AU$50,000, the lower bounds of the iNMB statistic were less than zero (-AU$1000), which suggests the intervention may not be cost effective. A cost-effectiveness acceptability curve of gains in QALYs shows that, at a willingness to pay of AU$50,000, the reference case intervention would have a 41% probability of being cost effective (Figure 4). A cost-effectiveness plane shows the probability distribution of costs and outcomes generated by bootstrap sampling (Figure 5). The results are distributed across quadrants one and four, showing the intervention was more costly and more effective, but also more costly and less effective, respectively. The cardiovascular fitness outcome for the intervention versus control group was a 19 second reduction in walking time over 400 metres (95% CI 3.95-42.0). The incremental cost per second was AU$29 (95% CI $13-$110).

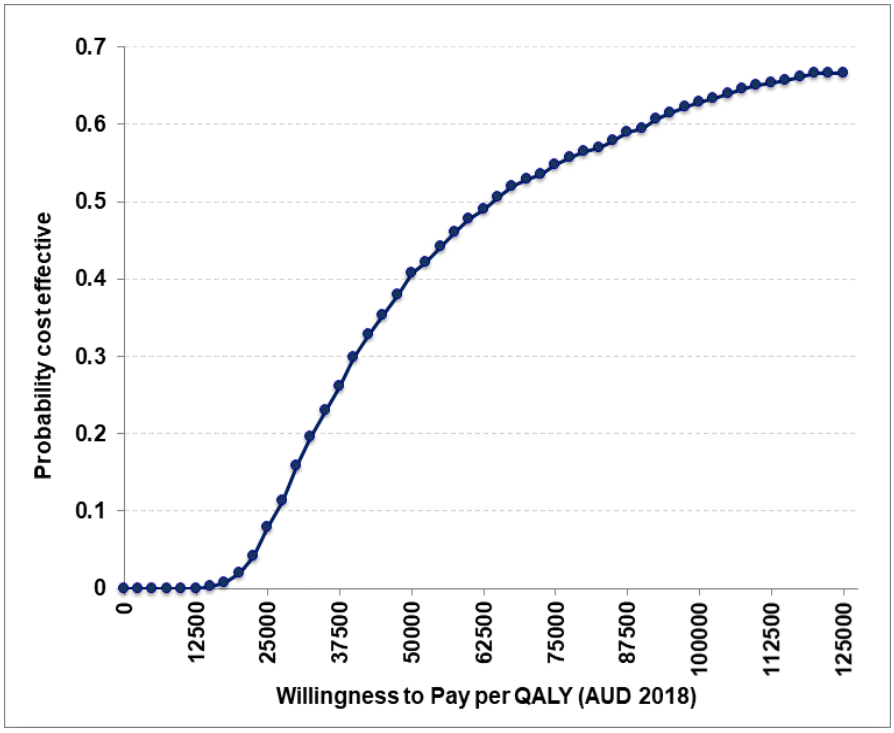


Figure 4 Cost-effectiveness acceptability curve

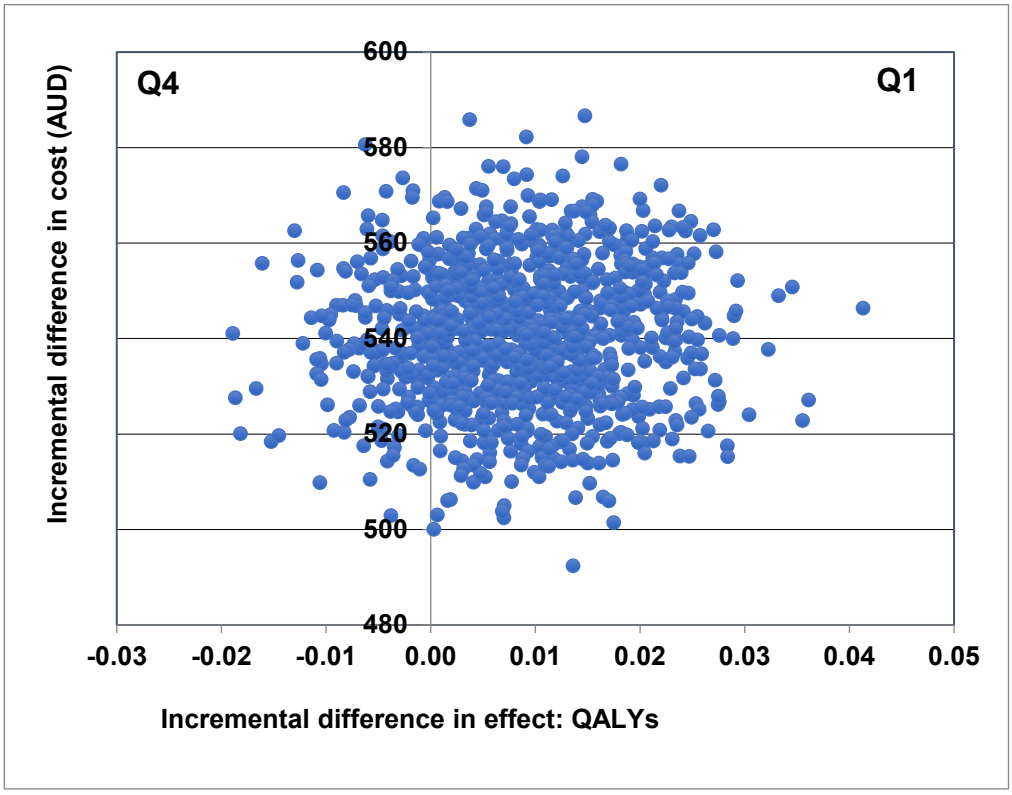


Figure 5 Cost-effectiveness plane

6.3.3 Univariate sensitivity analysis

For the primary outcome, QALYs, SA1 increased the mean magnitude of effect (0.0085) to the upper confidence interval limit (0.0256), resulting in a cost per QALY gain of AU$21,307. SA2 presents the societal perspective which, at an incremental

cost of AU$1012 results in a cost per QALY gain of AU$119,059. SA3 reduced the cost of implementing the intervention which resulted in a cost per QALY gain of AU$41,882. SA4 extended the impact of the intervention to 12 months (6-month supervised intervention + 6-month home-based intervention with exercise booklet) and resulted in a cost per QALY gain over 12 months of $32,051.

6.3.4 Scenario analyses

Scenario 1 varied costs of implementing the intervention in a real world setting such as a community-based program with increased numbers of participants per session, MBS item numbers to calculate AEP time and clerical awards to cost administrative duties, resulting in reduced implementation costs and a cost per QALY gain of AU$31,175. In Scenario 2, which incorporated the use of an in-house exercise gym at a private cancer clinic, the cost per QALY gain of the intervention was AU$19,752.

6.4 Discussion

In this study, patient-level data were used to explore the cost-effectiveness of supervised exercise for long-term PCa survivors who had previously received radiation therapy and ADT as part of the TROG 03.04 RADAR trial. This is the first cost-effectiveness study of a RCT of a supervised exercise intervention for long-term PCa survivors. The intervention demonstrated significant improvements at six months in terms of improved cardiorespiratory fitness, lower-body physical function and increased muscle strength, suggesting it is effective in addressing many of the health risks confronted by long-term PCa survivors receiving ADT, which could potentially lead to hospitalization, reduced quality of life and increasing health costs into the future for this population.

The cost-effectiveness analysis assessed the value of the exercise intervention using QALYs gained and outcomes from the 400-metre timed walk. From a healthcare payer perspective, the incremental cost of the intervention was $546. The value of the ICER was AU$64,235 per QALY gained. For cardiorespiratory fitness and functional mobility, the ICER per second reduction in walking time in the 400-metre walk was AU$29. While this seems inexpensive and there is evidence that better performance in this test impacts on mortality, risk of CVD, functional mobility and functional disability, it is an intermediate and abstract outcome(252). There is no way to evaluate what this means for the patient and it therefore provides little useful information for a decision maker.

Very few cost-effectiveness analyses have been conducted of exercise for any type of cancer(238-245), of which, only one was cost effective(245) and one had a high probability of cost-effectiveness(240). Many of these studies had short term follow-up,

small sample sizes, adherence or persistence issues, effected little change in quality of life measures and involved costly interventions, all of which impacted on cost-effectiveness outcomes. Systematic reviews of economic evaluations of physical activity interventions have also noted that intensive exercise programs tend to be more expensive and thus less cost effective(260-262). The challenge with cost-effectiveness analysis of exercise interventions relates to consistently measuring the impacts of physical activity and the diseases or effects associated with not doing physical activity. Outcomes used to measure the impact of exercise tend to be intermediate such as increased walking speed, reduced body fat and increased muscle mass or muscle strength. The lack of long-term data is a contributing factor. It is likely that were such evidence collected, cost-savings based on reduced incidence of falls or fractures, metabolic and lifestyle diseases such as diabetes or CVD and cancer recurrence or progression, would contribute to the cost-effectiveness of exercise programs.

QALYs are the recommended method for measuring benefit in a cost-effectiveness analysis because they provide a common metric which enables comparison of effectiveness across a wide range of health conditions. However, there are challenges in using QALYs and the instruments used to derive the utilities from which QALYs are calculated(263, 264). As this study and others have shown, quality of life measures are not always sensitive to change, despite the beneficial outcomes of the trials(265-268). The incremental utility when converted to QALYs can thus be relatively small, which may impact on cost-effectiveness, particularly of an intensive intervention. However, it is often such interventions that are more effective(262, 269). Recipients of curative treatment for PCa are typically younger than those with more advanced disease and the RADAR cohort were well-functioning(36), which means there may also be a ceiling effect in terms of perceived benefit. Given that QALYs may not adequately capture all the benefits associated with cancer-related interventions, cancer MAUIs have recently been developed from which utilities can be derived that are more sensitive to the experience of cancer populations(270). In addition, broader measures of quality of life such as the e-QALY, that capture benefits other than health, are also being developed(271). These alternatives to currently existing MAUIs and broader measures of benefit may provide more sensitive measurements of quality of life for cancer patients and survivors in the future.

While the supervised exercise intervention for PCa survivors from the RADAR trial at 6-month follow-up was not cost effective at a willingness-to-pay threshold of AU$50,000, sensitivity analysis 4 (SA4), which showed maintenance of HRQoL outcomes at 12 months (after the 6-month home-based exercise program), reduced the cost of the program by almost half and brought the cost per QALY gained well

below the willingness-to-pay threshold of AU$50,000. If achievable in a real-world implementation, a similar intervention would potentially provide an attractive policy option. Similarly, interventions with reduced costs (SA3, S1 & S2) or improved HRQoL outcomes (SA1), also brought the cost per QALY below this threshold.

The cost-effectiveness of any intervention inevitably depends on decision makers and how they value the intended outcome for the relevant population. In this case, it is what policy makers are willing to pay for the improved cardiovascular fitness and functional mobility of PCa survivors given the potential impact this will have on their risk of chronic disease, falls and fractures and their consequent health resource use and productivity. There was no within trial evidence to determine the benefits associated with the significant trial outcomes, and while modelling might be an option, sufficient evidence to populate such a model is not currently available. Research has demonstrated the association between performance in the 400-metre walk test and mobility limitation, as well as CVD(252) and the cardiovascular toxicity associated with ADT(63, 78-81, 84, 85, 272). Numerous studies in the literature report on the health benefits of exercise(49, 141, 235, 236, 273, 274), particularly in relation to muscle strength and falls prevention and metabolic diseases like diabetes or CVD(173, 275-282). There is therefore potential for supervised physical activity to impact on the risk of falls, fractures, diabetes and CVD for PCa survivors resulting in cost savings associated with reduced health utilisation and medication use, improved productivity and quality of life.

This study is unique in that it is the first cost-effectiveness analysis of a supervised exercise intervention for PCa survivors previously treated with curative radiation therapy and ADT. Strengths of the analysis include a sound trial design, and conduct, analysis and reporting, which follow best-practice methods(230, 253). The economic analysis was conducted from a healthcare payer perspective, supplemented by a sensitivity analysis which adopted a societal perspective. The use of primary data permitted the measurement of variance around mean costs and outcomes without having to employ assumptions related to their distribution. The fact that the data were drawn from a RCT controls for possible confounding of the results. The costing included the costs of implementation of the intervention, as well as patient out of pocket costs. As there was no evidence to support cost savings from downstream resource use such as reduced medications, health service utilisation or productivity losses (only seven of the 100 participants were still working and only three full time), these were not included in the analysis. The retrospective nature of the evaluation and a six-month follow-up meant that it was impossible to determine post intervention

outcomes like cardiovascular events, falls, fractures, metabolic and lifestyle diseases or further improvement in outcomes for the intervention group.

6.5 Conclusion

The results of this supervised exercise intervention for long-term PCa survivors after curative radiotherapy and adjuvant ADT show the intervention is effective, but unlikely to be cost effective after six months at a willingness-to-pay of AU$50,000 per QALY. It is likely that evidence to support downstream cost-savings such as reduced medication and health service use, carer costs and productivity losses, would contribute to a more comprehensive cost-effectiveness analysis. A further six months of exercise via a home-based program maintained HRQoL benefits and represents a potentially cost-effective option for future implementation outside a clinical trial. Future RCTs should incorporate longer follow-up durations and collection of data to support modelling to capture future health benefits. Measures of quality of life or utility more sensitive to the impact of physical activity would also improve future economic evaluations.

Chapter 7 Exercise in preventing falls and fractures for men with prostate cancer receiving androgen deprivation therapy: a modelled cost-utility analysis

7.1 Introduction

In Australia, over 80% of men with prostate cancer (PCa) are diagnosed with Stage I (localised) or II (locally advanced) disease(234) and have a 5-year survival rate of almost 100%, whereas men with distant metastatic disease have a 5-year survival rate of 28%(128). For men with local and regional disease, this can mean dealing with the adverse effects of treatments such as androgen deprivation therapy (ADT) for many years, highlighting the importance of finding a cost-effective way of managing them.

A number of ADT adverse effects are components of frailty such as muscle loss, reduced muscle strength, walking speed or cardiorespiratory fitness (40, 283) that, through impaired physical function and associated fatigue(138), place patients and survivors of PCa at high risk of falls(284). Another adverse effect of ADT is bone loss, which contributes to a high risk of fractures in this population. Studies of men receiving ADT report significant bone mineral density (BMD) declines at all sites in the first year, (ranging from 1.8%-6.5% at the femoral neck and 2%-8% at the lumbar spine)(22), which progress, but at a slower rate, in subsequent years.

Prevalence of osteoporosis in men receiving ADT for PCa is high. Over 50% of patient will suffer from osteoporosis if treated with ADT for three years and over 40% will have osteopenia(285). A recent Swedish cohort study confirmed that patients with PCa receiving ADT have increased risk of incident osteoporotic fractures(286). Risk of fracture was most pronounced in younger patients (70 years) where ADT contributed to an almost three-fold risk of any fracture (HR 2.63 95%CI 1.99, 3.48; p<0.001) and an almost four-fold risk of hip fracture (HR 3.89 95%CI 2.51, 6.02; p<0.001) compared to patients with PCa not receiving ADT(286). Men with PCa receiving ADT thus represent a particularly vulnerable population at significant risk of falls and fractures.

For Australians over the age of 50, falls and fractures result in significant morbidity or even mortality, and are a considerable burden to the healthcare system and society(287). Falls can have serious consequences such as major fracture (defined as major osteoporotic fracture [MOF] of hip, spine, lower and upper arm)(288) or head injury. Minor injuries such as bruising, lacerations, sprains and strains can still cause considerable pain, reduced function and fear of falling, and generate significant healthcare costs(289). By 2022, the community costs of managing osteopenia and osteoporosis are predicted to increase by 33%, adding weight to the argument for funding to be directed towards lifestyle changes such as exercise to decrease the prevalence of osteoporosis in the ageing population.

Exercise has been shown to have an important role in managing many of the adverse effects of ADT for PCa(290), particularly in relation to key fall risk factors such as ADT induced musculoskeletal changes(49, 137), the potential to prevent fall related fractures and injuries(167), as well as reduce fear of falling, a strong predictor of falls(291). Recently revised exercise for cancer guidelines reported strong evidence to support improvements in physical function and moderate evidence to support improvements in bone health(51). However, without any CEAs of exercise in this population, there is no economic evidence to support the implementation of such guidelines.

Given the burden of falls and fractures and the increased incidence for men with PCa on ADT, the purpose of this paper is to determine the cost-effectiveness of exercise in preventing falls and fractures in this high-risk population. A modelled cost-utility analysis was conducted to address the absence of available RCT evidence for men receiving ADT for PC. Economic modelling is a timely and cost-effective method for providing decision makers with the information required to determine allocation of scarce resources. This study conforms to Consolidated Health Economic Evaluation Reporting Standards (CHEERS)(292) and economic modelling guidelines(221, 293).

7.2 Methods

7.2.1 Population, perspective, time horizon and cycle length

The target population was individuals 65 years or older living in the community with a diagnosis of non-metastatic PCa (Stages I & II) receiving curative radiation therapy (RT) and adjuvant ADT, a population representative of the men expected to receive the exercise intervention. The population was assumed to be similar to that of the men with PCa participating in the RADAR trial (Chapter 6), a well-functioning group of men (n=100) motivated to participate in the exercise training program, who are more likely to be comparable to the general population than other PCa populations (e.g. older or more advanced PCa)(36). The mean BMI (24.9 kg/m^2) was identical across both arms and adherence for the exercise arm was approximately 80% over the 12 months of the trial intervention. Based on this population, the mean age at commencement of the model was 68(36).

The rationale behind the model is that exercise, comprising twice weekly group sessions of resistance, balance and functional training, supervised by an accredited exercise physiologist (AEP), will reduce the risk of falls as well as the number of fractures and injuries sustained. These outcomes will translate into reduced treatment costs from health service use and hospitalisation, and improved quality of life. Given that Australia has a publicly funded healthcare system, a health system perspective

was adopted to measure the cost per quality adjusted life year (QALY) for the exercise intervention compared to no intervention or usual activity.

The model consisted of two arms. The intervention arm was 12-month AEP supervised exercise training conducted for 1-hour twice weekly in small groups of up to 10 participants. Training comprised a combination of moderate- to high-intensity resistance exercise using machines and aerobic exercise such as walking, cycling or jogging. The comparator arm or usual care was based on guidelines that healthcare providers advise their patients to perform 150 minutes of moderate physical exercise per week(50, 51). A three-year time horizon for the economic model was deemed appropriate to capture the effect of one year of exercise training and an additional two-year sustained effect of exercise in preventing falls(36, 294). The cycle length was three months, the period of time generally required to recover from a fall injury or regain close to pre-fracture health-related utility(295).

7.2.2 Model structure

The Markov model was designed to capture the natural transition between various health states. Individuals move between five Markov states in the model: 1) at risk of falling; 2) at recurrent risk of falling; 3) fracture; 4) non-fracture injury; and 5) death. The state transition diagram is depicted in Figure 6. All patients begin in the 'at risk of falling' state and remain there until they fall when they progress to fracture, non-fracture injury or death. Survivors then move to 'at risk of recurrent fall' state until they fall again, when they progress to fracture, non-fracture injury or death. Survivors then return to 'at risk of recurrent fall' each time after they fall.

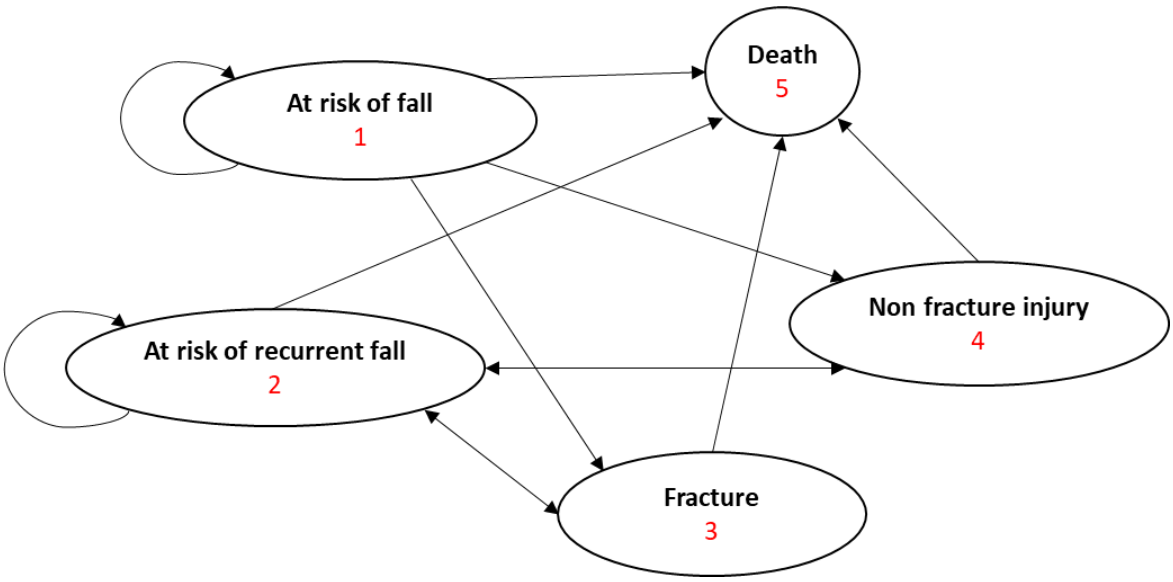


Figure 6 State transition diagram

7.2.3 Model input parameters

Model input parameters comprise transition probabilities, utilities and costs. Transition probabilities represent the probability of moving between the five states in the model and were based on published evidence of the highest level available. It was assumed that minor injuries or fractures do not cause death; major injuries or fractures may.

Health state utilities represent a preference value placed on a health state ranging from 1 for perfect health to 0 for death. Utility decrements reflect how an event such as a fall or fracture can impact negatively on a person's health state. The resulting utility can then be used to calculate quality adjusted life years (QALYs), where the utility represents the quality adjustment which is calculated over "life years" or the amount of time spent in that health state.

Costs were calculated for falls and consequent injury treatment. Assumptions made when calculating costs of treatment were as follows: a major injury or fracture refers to events requiring ED presentation and hospitalisation, followed by clinical and supportive care; minor fracture refers to a fracture requiring ED presentation and outpatient treatment in a hospital; minor injury refers to bruises, strains, cuts and sprains.

Exercise intervention cost was calculated with the assumption that cancer patients have access to 50 group sessions per year medical services funded by the Australian Medicare Benefits Schedule (MBS). Resource use costs included those costs specific to the intervention such as communication (telephone calls) with participants, material and printing costs (Appendix 5 - Supplementary file 1). Resources were valued using local or national costs where appropriate. All costs were reported in 2019 Australian dollars(232). All other resource use categories were valued using market rates.

Model input parameters were derived from numerous sources.

7.2.3.1 Transition probabilities

Evidence for number of men who experienced a fall (health state 1) and men who experienced a recurrent fall in the same year (health state 2) was based on a cross-sectional, survey-based study that examined falls and frailty in PC survivors with data on current and past users of ADT(284). This source most accurately represents our high fall risk population. Evidence from a recent systematic review of exercise for preventing falls in older people in the community was used to represent number of people experiencing fall related fractures (health state 3)(167). While this systematic review and meta-analysis(167) refers to the general population of community dwelling people 60 years and over, it provides high level evidence where there was an absence

of such evidence with regard to fall related fractures for PC patients receiving ADT. Probabilities of non-fracture injury (health state 4), type of non-fracture injury (major and minor) and type of fracture (major and minor) were derived from evidence for patients with PC receiving ADT in a large population-based cohort study(286). Evidence for death (health state 5) in the population age groups of interest were based on Scuffham, Chaplin and Legood(296) for fall related death and on Australian Bureau of Statistics Life Tables for age related mortality(297). Evidence for exercise in reducing the risk of falls, fall related fractures and non-fracture injuries, was drawn from two meta-analyses(167, 298).

7.2.3.2 Utilities

A baseline utility score representing the "well" state for men with PC (pre-fall) was based on a population of men who had been receiving radiation therapy with adjuvant ADT for two months(299). The health states in this study were measured using the Patient Oriented Prostate Utility Scale (PORPUS-U), a PC-specific indirect utility instrument which was used to elicit standard gamble utilities (PORPUS-U_{SG})(299).

Fracture utilities were based on evidence from the Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS)(295). Health related quality of life was estimated in this study using the EuroQoL EQ-5D-3 L questionnaire, a time trade-off (TTO) questionnaire. The values attached to each of the EQ-5D health states were based on the Australian TTO utility weights from general Australian population samples(295). The utility value applied in the model for fracture was the mean of the utility score at time of fracture and the utility score at three months or one cycle in the Markov model. Utility for major fracture was based on major osteoporotic fracture (MOF) as defined in the Fracture Risk Assessment Tool (FRAX) (hip, vertebral, wrist or humerus fracture)(288). Hip (40%) and vertebral fractures (30%) were the most common major fractures experienced by men with PC receiving ADT(300) and constituted a fracture group in the AusICUROS study(295). Utility for minor fractures was based on non-MOF fractures.

Utility for major non-fracture injury was based on a utility decrement for moderate traumatic brain injury (TBI), the second most common fall-related injury after hip fracture(301). Those aged between 65 and 75 tend to be at highest risk due to a more active lifestyle. Utilities for minor non-fracture injury, recurrent falls and fear of falling (FOF) were based on evidence from a study of falls and EQ-5D related quality of life of community dwelling seniors with chronic diseases(302). Exercise and the reduction in FOF was based on a Cochrane systematic review and meta-analysis of exercise for reducing FOF in older people living in the community(303).

7.2.3.3 Costs

Cost of treatment for fractures, both minor and major, were based on Watts et al.(304) and converted from 2012 to 2019 AUD. Costs for major injury (moderate traumatic brain injury as proxy) were based on the approach used by Pavlov et al.(305) with Australian costs calculated from the Independent Hospital Pricing Authority NEP 2019-20 for hospital care and costs of primary and community healthcare based on those calculated by Hall and Hendrie(306) converted to 2019 AUD. Cost for treatment of minor injury was calculated over 3-months using the IHPA for hospital costs and Hall and Hendrie(306) for primary and community healthcare costs. Given the vast difference in minor injuries and variation in the treatment required, it was assumed that at time of fall, 50 per cent of fallers attend ED and are discharged after treatment; 25 per cent see a GP and 25 per cent do not seek medical treatment(307).

The cost of the exercise intervention was based on AEP led supervised training comprising two 1-hour sessions per week over one year for men with localized or locally advanced PC, estimated from a healthcare payer perspective(308). Implementation costs included labour for participant registration (Clerks private sector award), a pre-intervention consultation with an AEP (MBS no. 81110), conduct of exercise sessions of up to 10 people by an AEP (MBS no. 10953), and a GP visit (MBS no. 23) to determine eligibility for participation in exercise training. Services provided by the AEP and GP were valued using the MBS(256).

7.2.4 Cost-utility analysis

Costs and outcomes are represented in the model as the mean value per state per cycle. All one year input parameters will be converted to three monthly values for the four cycles of the Markov model with the exception of cost of treatment which was attributed in the first 3-month cycle after the fall event only, when the majority of costs are incurred. Costs and QALYs will be aggregated for the time horizon and compared between the intervention and control to calculate incremental net monetary benefit (iNMB) or the difference in quality-adjusted life years (QALYs) times the willingness-to-pay threshold (AU$50,000), minus the difference in costs. All costs and outcomes were discounted at a rate of 5% per year, a commonly applied rate in Australia(309). Uncertainty in the model was explored via deterministic univariate and probabilistic sensitivity analysis. The analysis was conducted in TreeAge Pro Healthcare 2019 R1.1 and half-cycle corrections were used to adjust for overestimation of rewards in a traditional Markov model.

Table 15 Model parameters

Transition probabilities (12 months)	**Distribution**	**Mean value**	**(95% CI)**	**Source**
Fall in first year – control	Beta	0.36	(0.29, 0.43)	(284)
Recurrent fall in same year	Beta	0.65	(0.53, 0.77)	(284)
RR of fall in one year - exercise group	logNormal	0.76	(0.70, 0.81)	(167)
One or more fall related fractures - control	Beta	0.12	(0.09, 0.15)	(167)
RR of one or more fall related fractures - exercise	logNormal	0.44	(0.25, 0.76)	(167)
Major fracture (MOF)	Beta	0.62	(0.58, 0.66)	(286)
Minor fracture	Beta	0.38	(0.34, 0.42)	(286, 300)
Non-fracture injury	Beta	0.88	(0.87, 0.89)	(167)
RR of non-fracture injury-exercise	logNormal	0.70	(0.54, 0.92)	(298)
Major non-fracture injury	Beta	0.06	(0.055, 0.065)	(286)
Minor non-fracture injury	Beta	0.94	(0.93, 0.95)	(286)
Death from fall	Beta	0.023 60-64yrs 0.043 65-69yrs 0.065 70-74yrs	(0.015, 0.031) (0.033, 0.053) (0.062, 0.068)	(296)
Age-related mortality		Table 60-75 yrs		(297)
Cost (12 months)				
Treatment major injury	Gamma	$10,040	(9729, 10,351)	(305, 306, 310)
Treatment major fracture	Gamma	$20724	(20,082, 21,366)	(304)
Treatment for minor fracture	Gamma	$8797	(8524, 9070)	(304)
Treatment for minor injury (ED, non-admitted care, post discharge care)	Gamma	$1115	(1080, 1150)	(306, 310, 311)
AEP supervised exercise intervention	Gamma	$767	(743, 791)	(311)
Utility				
Baseline pre-fracture/injury	Beta	0.79	(0.78, 0.80)	(299)
Major fracture (MOF)	Beta	0.475	(0.47, 0.49)	(295)
Minor fracture ('non-hip, non-wrist, non-vertebral')	Beta	0.565	(0.55, 0.59)	(295)
Major fall injury (not fracture)	Beta	0.47	(0.46, 0.48)	(301)
Minor fall injury/no injury (not fracture)	Beta	0.765	(0.76, 0.80)	(302)
Recurrent fall (FOF)	Beta	0.72	(0.70, 0.74)	(302)
Recurrent fall exercise (FOF)	Beta	0.74	(0.72, 0.76)	(303)

Abbreviations: RR relative risk;MOF major osteoporotic fracture – hip, vertebrae, upper or lower arm; ED emergency department; AEP accredited exercise physiologist; FOF fear of falling

7.2.5 Univariate sensitivity analysis

Assumptions were tested over a range of values using univariate deterministic sensitivity analyses to assess the robustness of the uncertainty in the parameter estimates including variation in intervention and health service costs, probability of occurrence of events and utility values (Appendix 5 – Supplementary file 2).

7.2.6 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) involves random resampling of the model parameters followed by a recalculation of the NMB. The uncertainty around input parameters was modelled by fitting appropriate distributions to estimates obtained from the literature (Table 15). These were then used in a Monte Carlo simulation with 10,000 iterations to model joint parameter uncertainty. The results of the PSA are

presented as a cost-effectiveness acceptability curve (CEAC) which plots the likelihood an intervention is cost-effective against a range of willingness to pay thresholds.

7.3 Results

7.3.1 Base-case analysis

At a willingness-to-pay of AU$50,000 per QALY gained, the exercise intervention dominated, as it was less costly and more effective than usual care. The exercise intervention was cost saving at $1183 less than usual care and the incremental effect was 0.04 QALYs gained. The iNMB of the exercise intervention was $3,010 per patient, suggesting that the intervention is cost-effective (Table 16).

Table 16 Results modelled CUA of supervised exercise intervention (12 months)

Variable	Control group	Intervention group	Difference (95% CI)	NMB (95% CI)	iNMB (95% CI)
Mean cost	$4,135	$2,952	$1,183		
Mean QALYs at 12 months	2.06	2.10	0.04 (0.039 - 0.041)	$102,112 ($98,948 - $105,276)	$3010 ($2918 - $3104)

Abbreviations: NMB net monetary benefit; iNMB incremental net monetary benefit; QALYs quality adjusted life years

7.3.2 Univariate sensitivity analyses

The results of the univariate sensitivity analyses are shown in Figure 7. The most sensitive parameters with the greatest influence on the incremental net monetary benefit were cost of exercise, exercise induced fall risk reduction and probability of first fall. Only when the cost of exercise increases to amounts such as those in SA2a ($2338), SA4 ($2154) and SA4a ($3304) does the exercise intervention cease to be cost saving and become cost effective at a willingness-to-pay threshold of $50,000 per QALY gained (e.g. SA4a ICER $37050 per QALY gained) (Appendix 5).

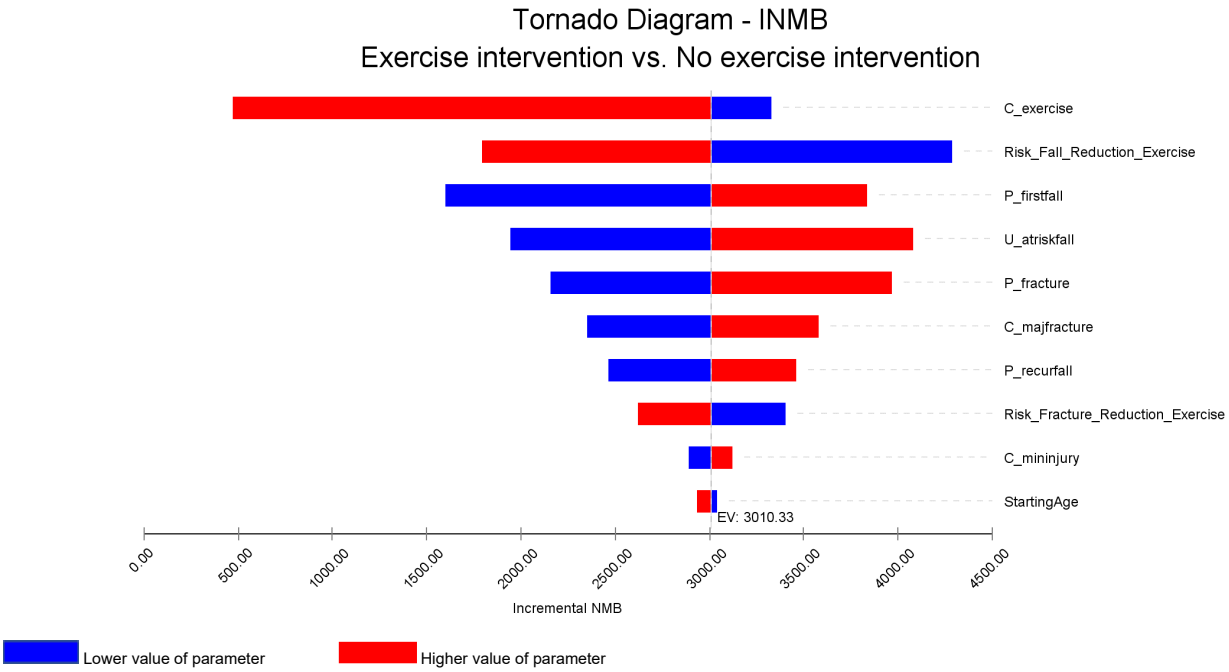


Figure 7 Univariate sensitivity analyses

7.3.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis with 10,000 iterations of the parameter distributions resulted in a NMB of $102,085 (95%CI $101,808 - $102,362). The probability that the intervention was cost effective at a willingness-to-pay threshold of $50,000 per QALY gained was 58 per cent. The cost-effectiveness acceptability curve (Figure 8) shows that exercise compared to usual care will be cost saving over a range of willingness-to-pay values per QALY gained.

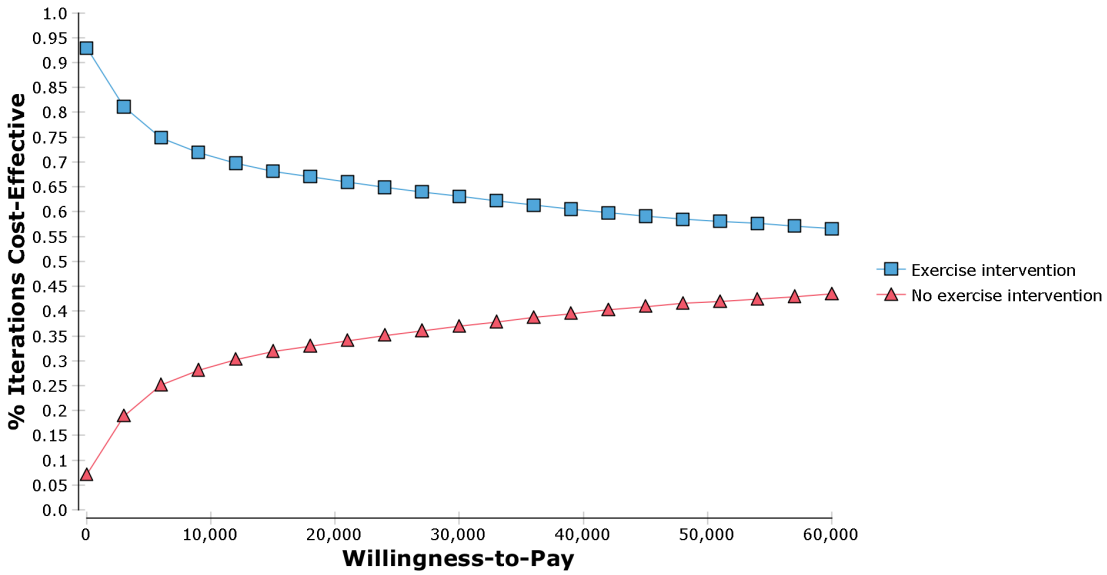


Figure 8 Cost-effectiveness acceptability curve

7.4 Discussion

This is the first economic evaluation conducted of exercise in preventing falls and fractures for men with PCa. The main finding indicates that exercise is cost saving at a willingness-to-pay of $50,000 per QALY gained. The model suggests that even if exercise interventions are provided by the health system twice weekly for a year and patient OOP costs (gym membership and travel costs) are included, the intervention would be cost effective at $37,050 per QALY gained. This is important information for policy makers when deciding which public health programmes to support. Univariate sensitivity analyses showed the results were sensitive to the effectiveness of exercise in reducing risk falls, the cost of the exercise intervention, and probability of first fall. Probabilistic sensitivity analysis showed a 58 per cent probability that the exercise intervention would be cost effective at a willingness-to-pay of $50,000.

A number of cost-effectiveness analyses of falls prevention exercise interventions for community dwelling older adults have been conducted, including both trial based(312, 313) and modelled or combined trial and model evaluations(314-317). However, none included men with PCa and they varied considerably in terms of population age (stratified and not), fall risk, the interventions included (group or home-based exercise, nurse or AEP led, multi-factorial or multiple intervention), the comparators, outcomes measured and model structures. The two trial-based CEAs did not incorporate a MAUI, so results were expressed as ICER per fall averted rather than QALYs gained, making comparison to our model impossible. The New Zealand trial which used nurses to conduct group resistance and balance exercise training people aged 80 years and older was more cost-effective, with an ICER of $AU1219 (2019) per fall averted(313), than the more costly UK multidisciplinary falls prevention program for people aged 70 years and older (including physiotherapy, occupational therapy, nurse, medical review and referral to other specialists) at AU$7679 (2019) per fall averted(312).

The results of this study are consistent with some of the modelled studies. Two of the four modelled CEAs of fall prevention programs were cost-effective in some form. One Markov model resulted in an ICER of AU$28,931 per QALY gained at a willingness-to-pay of AU$50,000, suggesting a public health intervention should be implemented. This result was based on a cost of $700 (2011 AUD) and a risk ratio for falls prevention of 0.75 for the general population aged 65 and over. The costs avoided of residential care admission, one arm of the model, would have contributed to the cost-effectiveness of this intervention(315). The second model incorporated a care pathway (GP screening for falls risk) with two interventions, a home-based exercise program (Otago) and a group exercise program (FaME)(316). The comparator was no

care pathway. Results were stratified for age. FaME was dominant for ages 65-89, whereas Otago was dominant in the 75-89 age group, but cost-effective for the 70-89 age group. In the other two models, group-based exercise was only cost-effective in the women only program in one study(317) and neither home-based nor group-based exercise was cost-effective in the other(314). Differences tend to derive from model structure. Only the FaME program achieved similar results to our study, but in a slightly older age group (70-89 vs 65-75). This is possibly because men with PCa receiving ADT are at higher risk than the general population of a similar age. The fact that our model included costs for all injuries treated, regardless of severity, may also have contributed to exercise being dominant in most scenarios analysed.

The results of this modelled study indicate that a public health program of AEP supervised exercise for fall prevention should be implemented for men with PCa who are receiving or have received ADT. A systematic review of exercise to prevent falls and fractures in older community dwelling people found that functional and balance exercise supervised by health professionals (e.g. accredited exercise physiologists and physiotherapists) is more effective in reducing rate of falls(167). Having access to this expertise is particularly important for men with PCa who may have been impacted by the adverse effects of ADT and at a higher risk of falls and fractures than the general population.

The strengths of this modelled evaluation are the use of QALYs as an outcome measure enabling policy makers to make comparisons across different health programs. The model structure reflects a realistic fall scenario by incorporating transition probabilities for falls, recurrent falls, utility decrements for fear of falling and a range of fall consequences such as fall related fractures and non-fracture injuries, both major and minor. The time horizon is relatively short and based on only one year of supervised exercise. However, sensitivity analyses doubling the time horizon to a 6-year time frame almost doubled the NMB and the exercise intervention maintained its dominance. Incorporation of longer follow-up to collect data on the impact of ADT induced metabolic changes such as diabetes, cardiac and vascular disorders, for example, and their associated treatment costs is likely to contribute to more cost-effective outcomes. Men similar to the population in this study can maintain the benefits of six months supervised exercise with home-based exercise(36). Many men find the health and wellbeing benefits, camaraderie and masculinity enhancing aspects of group exercise rewarding and continue to exercise beyond intervention timelines. For these men, the time horizon for exercise and the associated benefits would be extended, potentially enhancing cost effectiveness (34, 318). This would also suggest the results of our model are conservative.

Where there is an absence of individual level patient data, models must utilise numerous sources to derive evidence. As with any model, not all model inputs were drawn from the PCa population. In the absence of evidence for men with PCa, evidence from comparable populations and from the highest level sources available, such as systematic reviews and meta-analyses(167, 298, 303) were used.

7.5 Conclusion

This is the first cost-utility analysis of exercise in preventing falls and fractures for men with PCa treated with ADT. Supervised exercise is likely to improve quality of life and be cost saving in this vulnerable population. These findings strongly suggest that a public health program of AEP led exercise for falls prevention should be implemented for men with PCa who are receiving or have received ADT. This model is likely to be applicable to other cancer populations, other disease populations and older adults in the general population.

Chapter 8 Thesis results and discussion

This chapter is a summary of the thesis results and the work carried out in this doctoral research. The first section is a reiteration of the overall aims and objectives of the thesis. The key questions and summary of the results is presented in the second section. This chapter concludes with discussion of the research findings, implications, limitations and future directions.

8.1 Study aims and objectives

The aim of this research was to examine the cost-effectiveness of supervised exercise training in addressing the adverse effects of androgen deprivation therapy (ADT) for prostate cancer (PCa). The first objective was to identify the incidence of the most common adverse effects of ADT. Given the economic basis of the thesis, and the additional cost to treatment of managing ADT toxicity, the next objective was to examine the role of exercise in managing these adverse effects as a potentially cost-effective approach.

The approach taken was to conduct economic evaluations of two randomised controlled trials (RCTs) of exercise interventions for men with different stages of PCa (1. metastatic; and 2. localised and locally advanced). Due to the time limitations inherent in a PhD and the availability of data for this population, economic analyses were conducted on published RCTs. Given the limitations of conducting economic analyses of clinical trials, such as the lack of data (costs, outcome data applicable to economic analysis), short term follow up and small sample size, and armed with evidence of the important role of exercise in improving physical function for men receiving ADT for PCa, a modelled economic analysis was also conducted to determine the longer term impact of exercise in reducing falls and fractures for this population.

The four questions being addressed by the research were:

1. What is the risk or incidence of the most common adverse effects of ADT for PCa patients? (Chapter 2)
2. What is the role of exercise in managing these adverse effects? (Chapter 3)
3. What is the cost-effectiveness of exercise in managing the adverse effects of PCa?
    - CEA 1: What is the cost-effectiveness of exercise in the management of advanced PCa or bone metastatic disease? (Chapter 5)
    - CEA 2: What is the cost-effectiveness of exercise in counteracting the long-term adverse effects associated with ADT for localised/locally advanced PCa? (Chapter 6)

- CEA 3: What is the cost-effectiveness of exercise in reducing falls and fractures for men with PCa receiving ADT? A modelled cost-utility analysis. (Chapter 7)

4. What are the implications of exercise in the management of adverse effects of ADT for PCa? (Chapter 8)

8.2 Results: Responding to the study questions

8.2.1 What is the incidence of the most common adverse effects of ADT for PCa patients?

A systematic review of existing systematic reviews (n=25) is presented in Chapter 2, supplemented by evidence drawn from individual adverse effect studies where no systematic review existed (n=14), generated incidence evidence for nine adverse effect groups and 19 sub-groups, classified according to the common terminology criteria for adverse events (CTCAE)(17). Statistically significant increased risks were evident for 17 out of 19 adverse effect sub-groups as experienced by PCa patients and survivors (Appendix 2).

8.2.2 What is the role of exercise in managing these adverse effects?

A rapid review was undertaken and presented as Chapter 3, using the same CTCAE classifications applied in Chapter 2, revealed strong evidence for exercise in improving body composition (particularly, muscle strength and lean mass), physical function and fatigue. Moderate level evidence was also found for exercise in mitigating the bone loss, sexual dysfunction and psychosocial effects (anxiety, depression, HRQoL) associated with ADT. The second part of the rapid review, designed to address the current lack of PCa data, showed strong exercise as medicine evidence in other populations to support the role of exercise in managing the adverse effects of ADT for PCa.

8.2.3 What is the cost-effectiveness of exercise in managing the adverse effects of ADT for PCa?

Androgen deprivation therapy (LHRH agonist or orchiectomy) is used broadly in the treatment of PCa. Given the different stages and associated treatments and the varied capacity for exercise amongst patients, particularly for those receiving ADT for metastatic disease versus men receiving neo adjuvant or adjuvant ADT alongside curative treatment, we conducted economic evaluations of both these patient types.

8.2.3.1 Cost-effectiveness of exercise for men with bone metastases secondary to PCa

Prostate cancer patients with bone metastases are an important population as they tend to suffer considerable adverse effects associated with long-term ADT such as muscle atrophy and functional impairment, often exacerbated by subsequent

treatments like chemotherapy. These patients are at significant risk of falls and fractures. A considerable number of men with metastatic PCa (40-50%) will experience a skeletal-related-event (SRE), and per patient average lifetime cost for these men who experience one or more SREs is 50% higher than the cost of matched controls who remained SRE free(319). However, exercise intervention studies tend to exclude men with bone metastases due to the risk of fragility fractures; medical practitioners are often reticent for their patients to participate and patients are similarly disinclined. It is therefore difficult to recruit trial participants in this population and sample sizes tend to be small.

Two such RCTs have been conducted to date; the first, a preliminary study designed to test safety and efficacy of exercise in this population with a sample size of 20 (10 men in each arm; exercise and usual care or a recommendation to exercise)(34). SF-36 HRQoL data was collected which can be converted to utilities for use in cost-utility analysis (CUA). The second and more recent RCT extended the preliminary RCT, recruiting 57 participants between 2012 and 2015. This trial was an evaluation of the efficacy and safety of a multimodal exercise program comprising resistance, aerobic and flexibility training three times per week(147). However, the primary outcome measure was the SF-36 physical function subscale; other SF-36 subscales were not collected, so without the complete set of data, it wasn't possible to calculate a utility score or derive a QALY measure. In the absence of this data, the preliminary RCT was used to determine whether the exercise intervention was cost-effective compared to usual care. Given the small sample size and associated uncertainty, a value of information (VOI) analysis was conducted to examine the need for and value of a larger trial to collect the required evidence for a more comprehensive CEA.

This first within-trial CEA of supervised exercise training for men with metastatic PCa resulted in an incremental cost-effectiveness ratio (ICER) of $133,509 per QALY gained and a 30% probability of being cost-effective after three months at a willingness-to-pay of AU$50,000 per QALY (Chapter 5). VOI analysis resulted in a population EVPI of $971,520 which represents the upper-bound expected benefit of future research, suggesting further research is likely to be cost-effective to conduct.

8.2.3.2 Cost-effectiveness of exercise for long-term PCa survivors (>5years post diagnosis) from the Randomised Androgen Deprivation and Radiotherapy trial

Men with early stage PCa (Stages 1 and 2 - localised) represent a significant proportion of PCa population (82%) and, due to longer survival rates, can receive ADT and suffer the adverse effects over many years(320). The second within trial CEA involved a multi-centre RCT of exercise in long-term PCa survivors (>5 years post

diagnosis) who had received curative radiation therapy and adjuvant ADT (Chapter 6). This RCT was designed to determine the effectiveness of six months of supervised exercise training followed by six months of home-based exercise (with an instruction booklet)(36). The incremental cost per QALY gain at six months (supervised exercise training only) was AU$64,235 (dominated - $715,454). At a willingness to pay of AU$50,000, the supervised exercise intervention had a 41% probability of being cost-effective. At 12-month follow up (6-month supervised intervention + 6-month home-based intervention with exercise booklet), the resulting cost per QALY gain is $32,051 (dominated - $399,153) because the six-month QALY gain is maintained at no further cost, making the combined (supervised + home-based) intervention cost-effective at a WTP of AU$50,000.

8.2.3.3 A modelled cost-utility analysis of exercise in preventing falls and fractures for men with localised and locally advanced PCa.

In order to address some of the challenges encountered in within trial analyses and the lack of available RCT evidence for men in this high-risk population, a modelled CUA was conducted. We chose to focus specifically on falls and fractures as an outcome of the ADT adverse effect physical function for several reasons. The link between exercise and body composition and physical function is clearer than with other adverse effects such as metabolic syndrome, CV disease, and depression which can be confounded by other variables such as diet, pre-existing disease and comorbidities. This decision was supported by advice received from exercise physiologists and clinicians. A rapid review of the role of exercise in managing ADT adverse effects is presented as Chapter 3, also revealing strong evidence of the effect of exercise on lean mass, muscle strength, physical function and fatigue, attributes that have the potential to prevent falls as well as mitigate the resulting injury.

A decision analytic Markov model was developed in TreeAge (2019 R1.1) to evaluate the cost effectiveness of an exercise intervention in preventing falls and fractures for men with PCa receiving ADT. The target population was individuals 65 years or older living in the community with a diagnosis of localised and locally advanced disease, normally treated with curative radiation therapy and adjuvant ADT (a population representative of the men expected to receive the intervention), who have a high probability of survival(36, 234). The cost-effectiveness model has two arms to compare the health benefits in quality-adjusted life years (QALYs) and costs of treatment associated with the exercise intervention and those receiving a recommendation to exercise. A combination of sources (e.g. clinical data, systematic reviews and meta-analyses, population-based studies) were used in the development of the model. Costs, transition probabilities and utilities were based on published

evidence of the highest level available. Costs and outcomes were represented in the model as the mean value per state per cycle. The cycle length was three months and the model terminated after three years, one year for the duration of the exercise intervention and the following two years to capture the sustained effect of exercise in preventing falls(36, 247-250, 294).

At a willingness-to-pay of AU$50,000 per QALY gained, the exercise intervention dominated, as it was less costly and more effective than usual care (a recommendation to exercise). The incremental cost of the exercise intervention was $1183 less than usual care and the incremental effect was 0.04 QALYs gained. The NMB of the exercise intervention was $102,112 ($98,948 - $105,276) and the iNMB was $3,011 ($2918 – $3104) per patient, suggesting the intervention is cost-effective.

8.2.4 What are the implications of exercise in the management of adverse effects of ADT for PCa?

Exercise in the management of adverse effects of ADT for PCa has the potential to impact on exercise medicine research and practice; nursing and allied health practice; medical practice; economic analysis and policy decision making; as well as on the health and wellbeing of PCa patients and survivors and their families. These will be explicated and discussed in section 8.3.2.1 below.

8.2 Discussion

8.2.1 Thesis findings

No comprehensive review of the incidence of adverse effects of ADT for PCa has previously been carried out. The systematic review of existing systematic reviews (n=25), supplemented by evidence drawn from individual adverse effect studies where no systematic review existed (n=14), generated comprehensive incidence evidence for nine adverse effect groups and 19 sub-groups, classified according to the CTCAE. Statistically significant increased risks were evident for 17 out of 19 adverse effect sub-groups as experienced by PCa patients and survivors. These adverse effects impact negatively on quality of life, contributing to risk of falls and fractures and chronic diseases like diabetes and cardiovascular disorders, increasing healthcare utilisation and downstream costs. The need for more clearly defined ADT adverse effects, greater understanding of their incidence, the potential for subsequent treatment costs and the need for cost effective management given the potential for adverse effects to add further costs to what is already expensive treatment were highlighted.

In 2019, the Exercise and Sports Science (ESSA) position statement and the American College of Sports Medicine (ACSM) guidelines were updated, emphasising

the importance of appropriate exercise prescription for cancer patients. These updates were well supported by extensive scientific evidence(50, 51). While Australian and International PCa survivorship guidelines support exercise for adverse effect management(52-54), no comprehensive review of the benefits of exercise in managing the adverse effects of ADT for PCa has been conducted. The rapid review revealed strong evidence for the role of exercise in improving body composition (particularly, muscle strength and lean mass), physical function and fatigue adverse effects. Moderate level evidence was also found for exercise in mitigating ADT associated bone loss, sexual dysfunction and psychosocial effects (anxiety, depression, HRQoL). More research is needed for other adverse effect sub-groups because data for the ADT for PCa population is currently either limited or non-existent. However, exercise as medicine evidence in other populations is strong and, with the exception of gynaecomastia and breast pain, there is increasing evidence to suggest that exercise has the potential to reduce and even prevent the adverse effects of ADT for PCa, improving survivorship outcomes.

Exercise as medicine is not only effective in addressing the adverse effects of ADT for PCa, research also shows an association between exercise and risk of advanced and fatal disease(198). Men who participate in vigorous exercise, or had high levels of occupational and/or recreational physical activity, had reduced risk of advanced PCa and aggressive PCa(198). For men already diagnosed with PCa, exercise is associated with improved survival, reduced risk of progression and all-cause mortality. Such survivorship evidence extrapolated over the long term has the potential to reduce healthcare utilisation and PCa treatment costs contributing to more cost-effective outcomes for exercise interventions. Vigorous activity is also associated with lower risk of PCa mortality for this population(37). While more evidence of the effectiveness of exercise is needed for some adverse effects to strengthen the evidence-base, exercise medicine has the potential to provide a cost-effective alternative to other treatments (Chapter 3).

Despite the growing evidence of the important role of exercise as an essential part of any cancer treatment and care plan, uptake, adherence and implementation still needs to be addressed beyond the clinical trial period, when there is limited Medicare or private health insurance coverage for exercise medicine. While many healthcare professionals and men with PCa support exercise medicine, one study identified two major barriers to translation outside a hospital/clinic environment: traditional values in oncology and financial support from government(57). It is not uncommon for clinicians to be skeptical about the effectiveness of exercise,

disregarding it or considering it a fad. This is also reflected in the conservative values of government which tend to favour pharmaceuticals over lifestyle interventions.

Economic evaluation plays an important role in informing healthcare decisions. Cost-effectiveness analysis of effective programs, especially those based on the outcomes of randomised controlled trials (RCTs), are important sources of information for policy makers and essential tools to support the translation of research into practice. A rapid review of the literature from 2000 to June 2019 identified only eight cost-effectiveness analyses (CEAs) of exercise interventions for older community dwelling adults, none of which included interventions for PCa (238-245), yet PCa is the most common non-skin cancer in Australian men(234). Patients and survivors represent a particularly vulnerable population, especially those treated with ADT due to the number of associated and often long-lasting adverse effects. These can add considerable costs to treatment and reduce quality of life, highlighting a need to evaluate the cost- effectiveness of exercise in the ADT for PCa population. This gap is addressed in Chapters 5-7.

The two within trial CEAs (Chapters 5 and 6) included in this thesis provided an opportunity to examine the available data and investigate approaches to economic evaluation of exercise interventions for patients and survivors of PCa treated with ADT. There are advantages to conducting economic analyses alongside RCTs; the internal validity provided by the trial design such as blinding and randomisation reduces the potential for bias and makes it easier to attribute an effect to the intervention being compared. There is also the opportunity to collect patient level data on costs and outcomes and the likelihood that conducting an evaluation alongside a trial will be less costly than funding a stand-alone economic evaluation(321).

Both within trial cost-effectiveness analyses conducted as part of this thesis demonstrated that supervised exercise in the short term (3-6 months) is unlikely to be cost-effective. In the first CEA (Chapter 5), there was a 30% probability that an exercise intervention for men with bone metastases would be cost-effective at a willingness-to-pay per QALY of AU$50,000. This preliminary RCT with a small sample size provided the opportunity to conduct an early economic evaluation and value of information (VOI) analysis. The results showed that further research involving a larger trial would be cost-effective. Early economic evaluation and the use of VOI analysis is important because there is always uncertainty in economic analyses and in the decisions they inform. VOI is a systematic approach to measure this uncertainty and quantify the value of further research in reducing uncertainty. The second CEA (Chapter 6) was based on a 6-month supervised exercise intervention which, at a willingness-to-pay of AU$50,000, resulted in a cost per QALY gain of $64,235 and a

41% probability of cost-effectiveness. However, a 6-month home-based intervention immediately following the supervised intervention maintained QALY outcomes over 12 months and lowered the cost per QALY gained to $32,051, making the combination intervention cost-effective at a 57% probability of cost-effectiveness.

Typically, exercise medicine RCT sample sizes for these populations are small and there are associated levels of uncertainty. There are two main reasons for the small numbers. The first relates to the purpose of exercise RCTs, which is usually to determine the effect of exercise on a physical or biological outcome, like cardiorespiratory fitness, physical function, fat mass, lean mass, bone mineral density and so on. In most cases, changes in such outcomes can be determined in three to six months, so longer follow-up is unnecessary. Related to the purpose of RCTs is short funding time frames. Thus, it can be difficult to recruit eligible participants with cancer within the required time frame. This is particularly true for patients with advanced cancer and/or bone metastases due to comorbidities and the perceived risk of fragility fractures.

Cost and outcome data, such as downstream costs like health utilisation, medicines, allied health services and benefits like QoL, which are often not collected as part of an RCT, also impact on cost-effectiveness results. Interventions are generally conducted for three to six months, which is insufficient time to capture many of the benefits of exercise measurable in an economic analysis. The economic impact of exercise in reduced health utilisation, fewer medicines or greater benefits from improved QoL and reduced incidence of chronic disease that may become apparent over a longer time frame are not captured, so exercise appears to be less cost-effective without the inclusion of such data in the analysis. This situation is exacerbated for a cancer population grappling with a diagnosis, at the beginning of treatment and possibly suffering from the ill effects of the disease, cancer related anxiety and/or treatment.

The challenges associated with RCTs, small sample sizes, short follow up and a lack of data most suited to economic analysis, led to a modelled economic evaluation. Modelling provides a framework for synthesising the available evidence from a range of sources rather than relying on a single RCT to address uncertainty. Decision rules can be applied to determine the optimal alternative based on the evidence. The results are, however, dependent on the availability of data and the assumptions that underlie or form the structure of the model. Modelling is important, particularly when there are resource allocation decisions to be made, providing that the methods employed are sound. Based on findings from the systematic review (Chapter 2) and the rapid review (Chapter 3), which showed strong evidence to support the use of exercise in mitigating

ADT induced decline in body composition and physical function, the third economic evaluation was a modelled CUA of supervised exercise to address the risk of falls and fractures in the ADT for PCa population (Chapter 7). Model inputs (costs, transition probabilities and utilities) were derived from a combination of sources. Little real-world data around transition probabilities and utilities exists in the ADT for PCa population, so proxy data from like populations such as men with osteoporosis and older (65+ years) community-based populations were used. Results of the CUA of a 12-month exercise intervention to prevent falls and fractures for men with PCa modelled over three years showed that the intervention was cost saving compared to usual care (a suggestion to exercise). The drivers of the model were the effectiveness of exercise in reducing the risk of falls, the cost of exercise and the probability of first fall. Probability sensitivity analysis showed the probability that the exercise intervention was cost effective at a willingness-to-pay threshold of AU$50,000 per QALY gained was 58 per cent. This result provides strong evidence to support exercise prescription, particularly for vulnerable populations such as men with PCa receiving ADT who are at high risk of falls and consequent fractures or injuries.

In cost-effectiveness analysis, QALYs are the recommended approach to estimating the benefits of an intervention because they address heterogeneity by providing a common metric that enables comparison of effectiveness across a wide range of health conditions. However, there are challenges in using QALYs and the instruments used to derive utilities, particularly for older or chronically ill populations(263, 264). Questions regarding willingness-to-pay thresholds for cancer survivors and the possibility of giving greater weight to QALYs achieved in the later stages of terminal disease have been raised(269, 322). However, this highlights equity considerations, as to whether health can be distributed in a fairer way and how, a topic long debated in the literature(323, 324).

As the economic analyses in this thesis and others have shown, HRQoL measures are not always sensitive to change and the estimated QALY gain derived using a MAUI may not accurately reflect the experience of the patient, despite the beneficial outcomes of the trial(241, 242, 244, 265-268, 325). Given the characteristics of the study population, it may be unreasonable to expect a direct QALY benefit, particularly within the time constraints of the trial. Patients may not perceive a great change in wellbeing due to the short time frame or other factors like the impact of illness or concerns associated with a cancer diagnosis. The increase in utility when converted to QALYs can thus be relatively small, impacting on cost-effectiveness, particularly of a more intensive and costly intervention. In addition, MAUIs used to derive utility scores from which QALYs are

calculated for CEAs may not be sensitive to the benefits of exercise and may not capture the impact of exercise. For example, the scores for exercise relevant subscales can be diluted in a composite HRQoL tool by responses to other subscales.

Given that QALYs may not adequately capture all the benefits associated with cancer related interventions, there has been increased interest in alternatives or changes to QALYs(271, 325) or the development of condition-specific preference-based MAUIs(270, 326). An alternative for future studies, once such instruments have been validated, may be to use a new preference-based MAUI like the Australian specific European Organisation for Research and Treatment of Cancer EORTC quality of life utility measure-Core 10 dimensions (QLU-C10D) derived from the EORTC quality of life questionnaire for cancer patients (QLQ-C30)(270). While this instrument is more sensitive to utility decrements associated with cancer than more generic measures, it is focused on decrements associated with chemotherapy, not ADT. A new version of SF-6D, SF-6Dv2 for SF-36v2 has recently been developed which improves the classification of physical function and may contribute to more sensitive results in relation to utility for exercise interventions in the future(327). Another alternative may be the e-QALY, a broader measure of quality of life, which is being developed by researchers at the University of Sheffield(271). The e-QALY has the potential to improve the sensitivity of the QALY to capture the broader benefits of treatments for PCa patients receiving ADT.

In summary, the current research has comprehensively identified the incidence of the adverse effects of ADT and the important role of exercise in managing them. Economic evaluation of exercise medicine for PCa patients and survivors is in its infancy and this series of investigations represent the first economic analyses conducted, internationally. Results of two CEAs of exercise medicine RCTs demonstrated the need for more data and longer follow up and raised questions about QALYs as an outcome measure for exercise in the PCa population. Results of the modelled CUA showed supervised exercise was cost saving in preventing falls and fractures for men with PCa, an important finding for public health policy and research translation. The implications of this thesis have broad application and future research in PCa, exercise medicine and health economics can build on these findings.

8.3.2 Implications, limitations and future directions

8.3.2.1 Implications

The findings of this thesis have the potential to impact on exercise medicine research and practice, nursing and allied health practice, medical practice, economic analysis and policy decision making, as well as on the health and wellbeing of PCa patients and survivors and their families. The comprehensive identification of adverse effects of ADT and the role of exercise in managing them will contribute to the knowledge of exercise physiologists and physiotherapists treating PCa patients and survivors. For those conducting research, where there is an absence of strong data, there is an opportunity to conduct research on those adverse effects and strengthen the existing evidence base for the role of exercise in mitigation or management.

Oncology nurses and allied health practitioners (exercise physiologists, physiotherapists, nurses, psychologists, counsellors, social workers) play an important role in the treatment and supportive care of men with PCa suffering the adverse effects of different treatments. Men with PCa have identified support from peers, specialist oncology nurses and trusted partners as their preferred means of support(328). Nurses and partners can be instrumental in encouraging men to participate in exercise and nurses often actively refer men to allied health professionals as well as local support groups and organisations such as the Prostate Cancer Foundation of Australia (PCFA) to better address their unmet needs(157, 329). Aside from its physical and psychological benefits, exercise has also been shown to be an effective hook for men to participate in psychosocial support, where they otherwise may not get together and talk about their PCa or the difficulties they may be facing. The relationships men develop during exercise as a PCa patient can often persist after the transition to PCa survivor, when regular visits to their health professional team end and when many cancer patients may feel vulnerable and abandoned(330-334). This psychosocial support can also have a positive effect on the relationship dyad(318, 335). Short courses conducted by AEPs to disseminate information on how exercise is effective in managing adverse effects could be offered for nurses and allied health staff in hospitals and cancer clinics. Similar information sessions could also be offered to partners of patients.

For medical practitioners (e.g. GPs, oncologists, urologists), awareness raising of the full complement of adverse effects of ADT for PCa means that patients can be provided accurate information on the extent of the potential adverse effects they may experience and the impact on QoL. Exercise is particularly important for men receiving ADT, but findings with regard to the role of exercise emphasise the importance of providing exercise prescriptions to patients at PCa diagnosis, regardless of stage,

because exercise not only addresses adverse effects but slows progression and reduces morbidity and risk of mortality(37). Clinicians thus have an important role to play, particularly given the lack of any real understanding of the benefits of exercise in the community, aside from the fact that it is good for your health(336). Barriers to exercise in older people are numerous and common and when a suggestion to exercise is often all a health professional offers a PCa patient, there is little chance he will take the initiative(337, 338). Even an exercise prescription may not be enough; a referral to an AEP or contact with a PCa exercise group could perhaps be organized in the surgery and flexible arrangements that include a spouse or friend may help to inspire better uptake(328).

For health economists, the CEAs of RCTs (Chapters 5 and 6) have highlighted the importance of working with AEPs and clinicians when designing clinical trials, so data collection for economic analysis can be embedded in the trial data collection and prospective analysis carried out. Longer trial timeframes would assist in recruiting larger cohorts. Longer follow up would capture the physiological, physical and psychosocial benefits of exercise, which tend to take longer than three months to manifest and longer to impact on risk of falls and fractures, risk of metabolic and CVD, reductions in healthcare utilization, medicines, and so on. Value of information analysis was effectively used in an early economic evaluation of a preliminary RCT (Chapter 5) to determine that more research would likely be cost-effective, demonstrating the usefulness of this approach in measuring uncertainty and quantifying the value of further research.

In the two trial-based CEAs (Chapters 5 and 6), questions were raised with regard to the sensitivity and suitability in this population of currently available MAUIs used by health economists to calculate utility values and derive QALYs (e.g. SF-6D, AQoL, EQ-5D, HUI). Both RCTs used the SF-36 instrument to collect HRQoL data. There was little difference in QALY scores between baseline and follow-up or between control and intervention, suggesting there was insufficient time, or the instrument was not sensitive enough, to capture any change in exercise induced HRQoL. It is possible the SF-6D and other MAUIs may not be suited to measure the change in exercise-related QoL outcomes or the benefits of exercise may be diluted in a composite measure. These concerns deserve further investigation.

For policy makers, the findings of this research are an evidence base to better inform decision making with regard to the needs of men with PCa receiving ADT and their families. Raising awareness of the incidence of the numerous adverse effects and the effectiveness of exercise in addressing these should encourage policy makers to support funding of exercise interventions and their

implementation. With sound evidence supporting the cost-effectiveness of exercise in managing falls and fractures and benefits in relation to other adverse effects of ADT, there is a strong argument for adoption of a public health exercise program and the inclusion of regular supervised group exercise training for PCa patients and survivors as a Medicare Benefits Schedule subsidised service. Those who are receiving/have received ADT would provide a good test case given their vulnerability to falls and fractures. This type of program could then be extended to other cancer patients/survivors or the older (≥60 years) general population. Implementation strategies have shown to be effective in increasing uptake of exercise programs(339) and implementation science is important in ensuring implementation is not only effective, but cost effective. While there is currently a paucity of implementation evidence and deficiencies in the application of economic evaluation methods, this is a burgeoning field with a recently published guideline for the conduct and reporting of economic evaluations of implementation interventions in public health(340). Economic evaluation makes a critical contribution to exercise medicine research translation via its determination of the cost-effectiveness of exercise interventions and their implementation for policy makers.

Importantly, it has been shown that more research is needed to examine the effectiveness and cost-effectiveness of exercise as medicine to support translation into practice. Design and implementation presents challenges for exercise physiology practice, given the recognised need for prescription of exercise medicine to address variation in treatment effects, treatment intensity, patient comorbidities and fitness levels(50, 144). The transition to widespread application, clinically and post-clinically, presents a challenge, requiring collaboration between numerous stakeholders (patients, AEPs, nurses, psychologists, oncology specialists, GPs and policy makers) to achieve sustainable implementation strategies that promote access to and uptake of exercise for men with PCa(172, 200, 341). Co-location of exercise and cancer treatment has been suggested as a way of potentially addressing cost and adherence concerns(341). Economic evaluation also needs to include consideration of all aspects of intervention implementation.

Finally, the implications of this thesis for patients, survivors and families is that they receive more accurate information about all the current adverse effects of ADT for PCa and the important role of exercise in addressing them. The findings should encourage greater support for exercise medicine from medical practitioners which will mean men receive and act on exercise prescriptions, which has the

potential to minimize adverse effects, slow progression and improve quality of life and survival outcomes. Given the cost saving outcomes of exercise in relation to preventing falls and fractures, there is also the potential for exercise, via a Medicare subsidized public health program, to be more accessible for men with PCa. These benefits for PCa patients and survivors will have a flow-on effect for their partners and families.

8.3.2.2 Limitations

With systematic reviews and rapid reviews there is always the potential that a paper may have been missed or overlooked and excluded. In the specific case of ADT for PCa, the field is rapidly changing as new medicines are developed by pharmaceutical companies and approved for use by authorities like the Pharmaceutical Benefits Scheme (PBS) in Australia. New medicines can mean novel adverse effects depending on the nature of the drug, how it acts and the individual response a patient may have to it. Thus, there is a need to continually update the evidence on adverse effects. Similarly, the evidence base for the role of exercise in managing the adverse effects of ADT for PCa is currently incomplete and requires more research input.

Economic evaluation of exercise training in men with PCa receiving ADT is a nascent area of research and, as borne out in this program of research, only eight economic evaluations of exercise interventions for older populations had been carried out when the CEAs in this thesis were undertaken, none of which involved men with PCa, and few incorporating supervised exercise. Given the time constraints associated with a PhD, retrospective CEAs on published clinical trials were conducted. While results confirmed the effectiveness of exercise in managing ADT for PCa, the RCTs had not been designed with an economic evaluation in mind, so the costs were limited to those collected within-trial or estimated as accurately as possible where no data were collected and the benefits limited to those experienced within the trial follow up. When the follow up is 3-months to 6-months or even 12 months, it is difficult to capture cost savings and benefits. Benefits from exercise tend to accrue later than the time frame of a RCT, when a man who exercises doesn't develop metabolic adverse effects (which can lead to diabetes and CVD), bone loss (which can lead to osteoporosis and a greater risk of fractures) or declines in lean mass and physical function (which can lead to higher risk of falls and consequent fractures) to the same extent as a patient who doesn't exercise. When the outcomes of this treatment toxicity manifest, costs related to greater health service utilisation and associated medications are considerably higher and QoL considerably lower. It is likely to be the long-term cost savings from reduced health service utilization, reduced medication use and HRQoL

benefits of exercise that contribute most to the cost-effectiveness of exercise interventions.

There were also limitations associated with the SF-36 instrument used to measure HRQoL in both within-trial CEAs as it was not sensitive enough to capture the benefits of exercise or discriminate between the exercise and control groups. A number of reasons may have contributed to this result. The sample population may have been unusually fit and already at a ceiling they couldn't improve on or too unwell to effect a change within the time frame; the composite nature of the tool may have meant the results of other sub scales (not exercise related) may have diluted the exercise benefit; or the length of follow up may simply not have been long enough to capture any perceived improvement. It is also possible MAUIs like the SF-6D may not be suited to measure exercise related changes in HRQoL outcomes. Questions raised in the economic analyses could be addressed in further research and methods improved.

Economic modelling is a feasible alternative to economic analysis based on a single RCT, which is unlikely to contain all the relevant inputs, have long enough follow-up to capture exercise benefits or a large enough sample to be representative of the population. However, there is always a level of conjecture around any model input. Not all data used in the modelled CUA were derived from ADT for PCa patients. Data derived from osteoporotic or healthy older adult populations were used as proxies for transition probabilities and utility scores, where there was an absence of PCa data. The model time horizon was short and captured only falls and fractures and consequent treatment, not long-term effects like diabetes or CVD.

8.3.2.3 Future directions

Adverse effect findings need to be continually updated, particularly when new medicines are added to the treatment regimen. Similarly, as more research is conducted on the impact of exercise on different ADT adverse effects, existing evidence needs to be updated and new evidence added.

Future exercise medicine research should involve collaboration with economists at research design phase in order to ensure the required data is collected and the research design, including longer follow-up, will support a rigorous economic evaluation. Another potential solution to longer follow-up times, which can be expensive to achieve, is the consideration of epidemiological evidence, where evidence exists, that links intermediate and long-term outcomes. VOI analysis can be conducted to quantify the value of further research and optimise trial design.

Based on the outcomes of the within-trial CEAs, there is potential that a MAUI could be developed that is more sensitive to the benefits of exercise or better

discriminates between the quality of life of those participating in exercise and controls. Both RCTs measured HRQoL using the SF-36 and the SF-6D to derive utilities, and were found to be insensitive to change, so further exercise medicine economic analyses need to be conducted over longer time frames and possibly with different MAUIs, particularly new preference-based MAUIs such as the Australian specific EORTC QLU-C10D, derived from the cancer specific QoL questionnaire, EORTC QLQ-C30. A potential alternative may be the SF-6Dv2 or the eQALY, a broader measure of quality of life being developed at the University of Sheffield. With the increasing recognition of the importance of exercise medicine and its application in prevention, and across numerous health conditions and diseases, it is also possible that an exercise sensitive MAUI could be developed in the future.

The modelled CUA revealed a lack of real-world data for men with PCa and the need to develop an evidence base for this population to use in economic models. The falls and fractures model could also be modified for application in other cancer or disease populations or equally in healthy populations. Genuine ADT for PCa data from real world sources such as hospital databases could be used to strengthen the rigor of the model. Extrapolating the model over a longer time horizon to capture the impact of exercise on the reduced burden of metabolic diseases such as diabetes and CVD would also improve the model and contribute to more cost-effective outcomes.

8.4 Conclusion

This doctoral research is the first investigation of the cost-effectiveness of exercise medicine in managing the adverse effects of ADT for PCa. The incidence of a comprehensive list of adverse effects of ADT was examined, confirmed the role of exercise in managing many of these adverse effects and highlighted where more research is needed. Cost-effectiveness analysis of two RCTs identified limitations of within-trial CEA of published exercise interventions due to small sample size, insensitivity of currently available QoL instruments and short-term follow-up. These CEAs showed there was a low probability (30-40%) that supervised exercise is cost-effective in the short term (3-6 months), highlighting the need for collaboration between health economists and AEPs at the research design stage to ensure the required data is collected over longer time frames, reducing uncertainty in health economic outcomes. Application of VOI analysis in a preliminary RCT was used to estimate the value of additional evidence to reduce uncertainty, showing the benefit of early economic evaluation using this approach.

A modelled CUA demonstrated that exercise is cost saving in preventing falls and fractures in PCa patients receiving ADT for localized and locally advanced disease.

There is potential for this model to be developed further, improved by incorporating more PCa specific data, extrapolated over a longer time horizon and applied to other cancers, diseases or healthy populations.

The cost-effectiveness of exercise medicine in PCa is a nascent area of research with much scope for further research. There is potential to improve economic evaluation in this field and reduce uncertainty, methods which can be applied to the economic evaluation of exercise in other fields and for other diseases. Importantly, these findings provide strong evidence that exercise medicine should be more accessible for men with PCa, contributing to slower disease progression, less morbidity, increased survival and improved quality of life for PCa patients and survivors, their partners and families. Efforts should be focused on conducting more economic evaluation of exercise medicine for PCa, collecting more data specific to this population and incorporating methods of economic analysis suited to these interventions. Decision making based on rigorous economic evaluation is more likely to contribute to research translation and the implementation of effective and cost-effective public health exercise programs.

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Appendix 1 Systematic search (Chapter 2)

Search strings and databases utilised in search strategy

Ovid (Medline; PsycInfo); Elsevier (Embase)	1226
Prostatic Neoplasms/	
(androgen adj (deprivation or ablation or suppression)).mp. OR Gonadotropin-Releasing Hormone/ag, ai [Agonists, Antagonists & Inhibitors] OR Luteinizing Hormone/ag, ai [Agonists, Antagonists & Inhibitors] OR Androgen Antagonists/ or anti-androgens.mp. OR androgen receptor inhibitors OR adrenal androgen inhibitors.mp. OR goserelin OR leuprorelin OR triptorelin OR degarelix OR cyproterone acetate OR enzalutamide OR bicalutamide OR flutamide OR nilutamide OR apalutamide OR abiraterone acetate	
((side or adverse) adj (event* or effect*)).mp. OR complication*.mp. OR toxicity.mp.	
incidence.mp. OR rate.mp OR risk.mp	
limit to (english language and humans and yr = 2010 - Current [February 2019])	
“systematic review”.mp OR meta-analysis.mp	
Cochrane Library (Reviews, Protocols, Trials)	27
"androgen deprivation": ti,ab,kw	
"prostate cancer": ti,ab,kw	
("adverse effects" OR “side effects” OR complication* OR toxicity): Search All Text	
Limits: Publication Year from 2010 to February 2019, in Cochrane Reviews, Other Reviews and Trials (Word variations have been searched)	

Appendix 2 Summary of findings (Chapter 2)

First author, Year, Country	Study type	Cancer stage & treatment	Sample size (control group)	Outcomes/Incidence %, RR, HR, OR (95% CI)	Quality assessment/ Risk of bias
Kim 2019 Korea (69)	Systematic review & meta-analysis: includes prospective cohort studies	**Stage:** Localised or advanced PCa **Treatment:** orchiectomy, LHRH agonist, alone or combined (LHRH agonist + antiandrogen) 6-36 months ADT duration	Pooled analysis of 5 studies n=533 ADT: orchiectomy, LHRH agonist, anti-androgen Follow-up 1 year in 1 study; 2 years in 2 studies; 3 years in 2 studies. Men taking bone sparing agents not mentioned in 1 study, excluded in 4 studies (censored if initiated during trial in one study or allowed if osteoporotic in a second study).	**Mean difference in % change in BMD** **Lumbar spine:** 4 studies n=483 -3.60 (-6.72—0.47, *P* =0.02) **Femoral neck:** 5 studies n=515 -3.11 (-4.73—1.48, *P* =0.0002) **Total hip:** 4 studies n=483 -1.59 (-2.99—0.19, *P*=0.03)	AMSTAR 2 rating: Low
Ng 2018 Australia (97)	Retrospective cohort study using PBS data	**Stage:** Localised or advanced PCa **Treatment:** Any ADT ADT duration stratified into >1 & <1 year (For details see Table S3 in Ng et al.)	Random 10% sample of population 2003-2014 3689 men receiving first ADT between 2004 – 2010 Age: 92% osteoporosis cohort ≥65 years at ADT initiation Follow-up to 2014 **Control:** Age & sex matched cohort not receiving anti-neoplastic agents or having none of 9 comorbidities at baseline	Osteoporosis: aHR 1.65 (1.48-1.85) Sub analysis of ADT duration: Higher risk >1 year aHR 1.77 ≤1 year aHR 1.38 The PCa cohort had a significant, higher risk of developing most comorbidities, i.e. cardiovascular conditions, depression, diabetes, gastric acid disorders, hyperlipidaemia, osteoporosis & pain/pain-inflammation vs control groups	NOS rating: Good
Smith 2018 USA (104)	Phase III double-blind RCT	**Stage:** Non-metastatic CRPCa **Treatment:** Apalutamide	n=1207 men receiving ADT; (n=806) Age: 48-94 Median follow-up 20.3 months **Control:** placebo (n=401) Age: 52-97 Bone sparing agent 10% vs 9.7% (placebo)	Fracture 11.7% (apalutamide) vs 6.5% (placebo)	ROB 2 rating: Some concerns
Graff 2016 USA (105)	Multinational double-blind RCT	**Stage:** Chemotherapy naïve mCRPCa **Treatment:** Enzalutamide Median duration of treatment: <75 years16.7 (Enzalutamide) & 4.4 months (placebo); >75 years 16.6 (enzalutamide) & 5.0 months (placebo)	n=1717 **1.** <75 (n=1108); (42-74 years) **2.** ≥75 (n=609) (75-93 years) Follow-up: varied dependent on disease progression or death **Control:** placebo No clear differences between treatment groups regarding concomitant use of systemic corticosteroids, denosumab, & bisphosphonates.	Incidence rate of any fracture: Enzalutamide vs control by age group (<75 9.9% vs 3.6%) (≥75 15.8% vs 7.9%) & non-pathological fractures (<75 6.5% vs 1.8%) (≥75 10.1% vs 5.1%) Higher than placebo group for both age groups. **1. Enzalutamide <75** vs control; **2. Enzalutamide ≥75** vs control **Fracture: 1.** 9.9% vs 3.6% (RR 2.75)**; 2.** 15.8% vs 7.9% (RR 2.0); non-pathological fracture **1.** 6.2% vs 2.8% (RR 2.2); **2.** 8.7% vs 9.6% (RR 0.91) **Fall any grade: 1.** 7.2% vs 4.0% (RR 1.8); **2.** 19.2% vs 7.9% (RR 2.43); older vs younger 13.8% vs 5.6% (RR 2.5) **Fall requiring hospitalization: 1.** 0.9% vs 0.5% (RR 1.8); **2.** 2.2% vs 1.0% (RR 2.2)	ROB 2 rating: Some concerns

Shao 2013 USA (98)	Population-based linked data SEER-Medicare data	**Stage:** Localised PCa **Treatment:** ADT only; ADT + curative therapy; orchiectomy	n= 75 994 Age ≥66 1992-2007 Follow-up: 12 years Bisphosphonate use during follow-up (4.3%) **Control:** no ADT	26.83% developed at least one fracture; 8.8% required hospitalisation **Risk group:** > 58% of men in the high-risk group and 38% of men in the low-risk group sustained fracture; 31% of men in low-risk group No-ADT sustained fracture. **Treatment group:** For **ADT only**, fracture risk of men receiving 18 doses of GnRH agonist was HR 1.53 (1.44–1.62) for low-risk group and 1.27 (1.20–1.35) for the high-risk group compared to No-ADT. **ADT + other curative** treatments, fracture risk was 1.37 (1.27–1.49) for the low-risk group; 1.20 (1.09–1.33) for high-risk group. 22.3% of fractures in this study were hip fractures (assoc. with increased risk of mortality)	NOS rating: Good
Alibhai 2010 Canada (100)	Matched cohort study using linked admin. data	**Stage:** Non-metastatic PCa **Treatment:** LHRH agonists, non- steroidal or steroidal anti-androgens alone or in combination & orchiectomy ADT duration: at least 6 months continuous ADT	n=19,079 ≥66 years 1995-2005 **Control/reference:** Propensity score matched population non-ADT PaC Mean 6.47 years follow-up	ADT 9% vs non-ADT 5.9% had fragility fracture of spine, lower arm, hip/femur (aHR 1.65, 1.53-1.78, *p*<0.0001) (RR 1.52); Any fracture 17.2% vs 12.7% (aHR 1.46, 1.39-1.54, *p*<0.0001) (RR 1.35) ADT/non-ADT Elevated risk associated with age, prior osteoporosis, prior fragility fracture, prior dementia and prior bone thinning medication	NOS rating: Good
Wallis 2016 Canada (99)	Retrospective cohort study SEER & Medicare linked data	**Stage:** Localised PCa **Treatment:** Radical Prostatectomy +/-ADT; Radiotherapy +/- ADT ADT duration stratified for sub analysis: 6, 12 & 18 months	n=60,156 (14,403 RP; 45,753 RT); Age ≥65 years Median follow-up 6 years **Control/reference:** radical prostatectomy	aHR (95% CI) Primary treatment + ADT (adjusted for age, grade, race, marital status, comorbidity index, pre-diagnosis osteoporosis) Any Fracture 1.28 (1.16, 1.41; *P*<0.0001) Fracture requiring hospitalisation 1.32 (1.19-1.46; *P*<0.0001) No difference in risk of skeletal related events for patients receiving shorter durations of ADT whether threshold was 6, 12 or 18 months (Supplementary Table S8)	NOS rating: Good
Sun 2016 USA (101)	Population-based cohort study SEER-Medicare linked data	**Stage:** Metastatic PCa **Treatment:** GnRHa	n=3295 (1995-2009) Age ≥66 years Follow-up 12 months **Control/reference:** Orchiectomy	Any fractures incidence GnRHa 37.7% vs Orchiectomy 31.4% HR (95% CI) 0.77 (0.62, 0.94; *P*=0.01) sub analysis GnRHa duration 18-34 months 1.48 (1.17, 1.97; <*P* 0.001) ≥35 months 1.80 (1.45, 2.24; <*P* 0.001)	NOS rating: Good
Beebe-Dimmer 2012 USA (103)	Population-based cohort study SEER-Medicare linked data	**Stage:** Advanced PCa **Treatment:** GnRH agonist ADT duration stratified for sub-analysis:1-5 doses, 6-17 doses, ≥18 doses	n=80,844 Age ≥66 years diagnosed 1996-2003 Follow-up to December 2006 **Control/reference:** non-ADT PCa	M0 + GnRHa 31% increase (HR 1.31; 1.29-1.39) +ve relation between cumulative dose & fracture incidence. Higher increase in incidence of fractures for M1 (aHR 1.52; 1.36-1.67) HRs adjusted for recency of exposure & dose of ADT. Orchiectomy associated with 62% increase in risk of any fracture (aHR 1.62; 1.42-1.84) among M0 & 54% increase in M1 (aHR 1.54; 1.26-1.88). Fracture risk highest for men currently receiving or within 6 months (aHR 1.67; 1.56-1.78). Fracture risk for M0 men who had received fewer than 6 doses discontinued ADT more than 18 months ago (aHR 1.06; 0.99-1.14). Similar for M1 men. Mortality risks within 6 & 12 months or experiencing any fracture 8.3% & 12.2%, respectively. Fracture associated with two-fold increase in rate of death	NOS rating: Good

				(aHR 2.05; 1.98-2.12) & aHR 2.82 (2.68-2.97) for fracture requiring hospitalisation. Use of bisphosphonates overall prior to fracture 2.3%; 0.6% in non-metastatic patients and 18.2% in metastatic patients.	
Tsai 2017 USA (102)	Population-based cohort study	**Stage:** Advanced PCa **Treatment:** IADT	n=9772 men ≥66 years Follow-up: 5 years post ADT initiation **Control/reference:** CADT	IADT lower risk of fracture than CADT (HR 0.52; 0.38-0.70, *p*<0.0001)	NOS rating: Good
Haseen 2010 Ireland (67)	Systematic review: includes RCTs & cohort studies	**Stage:** Localised, locally advanced, advanced, metastatic **Treatment:** LHRH, GnRH, anti-androgen, orchiectomy	Pooled analysis 14 studies n=573 Baseline to last follow up; varied from 12 weeks to 96 weeks but more than 50% of studies had 12 months follow up Sub group analyses of ADT duration ≤3 months, ≤6 months, >6 months	**% change body weight:** 2.14 (1.35-2.94, P<0.00001); **% change BMI (95% CI):** 2.15 (1.16-3.14, P<0.0001); Increases in body weight and BMI more pronounced for treatment duration >6 months. **% change fat mass (95% CI):** 7.71 (4.27-11.15, P<0.00001); treatment duration varied from 3-12 months; all (7 studies) showed significant gains regardless of duration or treatment type. **% change lean mass (95% CI):** -2.82 (-3.64- -2.01), P<0.00001 Treatment duration varied from 3-24 months; loss reported in all studies (n=6)	AMSTAR 2 rating: Low
Bosco 2015a UK (64)	Systematic review and meta-analysis	**Stage:** All **Treatment:** Any ADT	9 studies: Pooled analysis of 4 cross sectional studies for MetS; 4 cohort & 1 cross sectional study for Diabetes ADT n=335 **Control:** No ADT n=594	RR 1.75 (1.27-2.41) MetS; RR 1.36 (1.17-1.58) Diabetes Need for further research on impact of type and duration of ADT.	AMSTAR 2 rating: Moderate
Wang 2016 China (83)	Systematic review and meta-analysis	**Stage:** mCRPCa **Treatment:** GnRH, combined androgen blockade, orchiectomy	8 studies n=157,588 follow up varied in cohort studies from 1 year to 6.47 years Control: No ADT, watchful waiting/active surveillance Sub group analysis: short duration ≥6 months; long duration >6 months	10.9% developed diabetes Diabetes RR 1.39 (1.27-1.53, P<0.001) sub group analyses show that GnRH (*P*<0.01), GnRH + anti-androgen (*P*=0.04), & orchiectomy (*P*<0.01), are significantly associated with risk of diabetes Longer duration significantly associated with risk of diabetes RR 1.39 (1.27, 1.53) *P*<0.00001	AMSTAR 2 rating: High
Bosco 2015 UK (63)	Systematic review and meta-analysis	**Stage:** not reported **Treatment:** GnRH agonist, orchiectomy, anti-androgen	Pooled analysis of 8 observational studies n=414,657 **Control:** No ADT	**GnRH agonists**: i. any type CVD: RR 1.38 (1.29-1.48); ii. Non-fatal IHD: RR 1.39 (1.26-1.54); iii. non-fatal MI or stroke: RR 1.57 (1.26-1.94); iv. fatal MI or stroke: RR 1.51 (1.24-1.84); **Orchiectomy**: i. any non-fatal CVD: RR 1.44 (1.28-162); **Antiandrogen**: i. Any non-fatal CVD: RR 1.21 (1.07-1.37)	AMSTAR 2 rating: Moderate
Jin 2016 China (68)	Systematic review and meta-analysis	**Stage:** Locally advanced, metastatic or recurrent hormone sensitive PCa (HSPCa) **Treatment:** IADT	Pooled analysis of 6 RCTs (n=4810) n=4,810 men with HSPCa **Control:** CADT	No significant diff for CV events: RR=0.95 (0.83-1.08) Association between low CV mortality & IADT: 0.85 (0.71-1.00) (n=4170)	AMSTAR 2 rating: Moderate
Magnan 2015 Canada (71)	Systematic review and meta-analysis	**Stage:** Locally advanced, recurrent, metastatic, mCRPCa **Treatment:** IADT	Pooled analysis of 15 RCTs n=6586 **Control:** CADT	**CVD death** HR 0.86 (0.73-1.02) 4 studies **Fatigue** HR 0.94 (0.60-1.48) 2 studies **Gynaecomastia** HR 0.63 (0.36-1.10) 6 studies **Hot flashes** HR 0.76 (0.57-1.00) 6 studies **Erectile dysfunction** 1.03 (0.74-1.43) - 4 studies **Decreased libido** 1.01 (0.95-1.07) - 2 studies	AMSTAR 2 rating: Moderate

				Depression 0.91 (0.39-2.13) - 3 studies	
Zhao 2014 China (84)	Systematic review and meta-analysis	**Stage:** All/any **Treatment:** GnRHa GnRHa + AA Orchiectomy	7 observational studies 129802 vs 165,605 control ADT & AMI: 6 studies, 129,802 ADT vs 165,605 control Control: No ADT or watchful waiting/active surveillance	**ADT & CVD (6 studies)** 1.10 (1.00, 1.21, P=0.06) **ADT & CVM (6 studies)** 1.17 (1.04, 1.32, P=0.01) **ADT monotherapy vs WW/AS for CVD (3 studies) & CVM (4 studies)** **CVD** 1.19 (1.08, 1.30, P=0.0004) **CVM** 1.30 (1.13, 1.50) **ADT & MI** 1.10 (0.97-1.26, P=0.14) **subgroup analyses for ADT type:** positive association for GnRH (RR 1.20, 1.05-1.38, P=0.008); AA alone (RR 0.88 0.81-0.96, P=0.002)	AMSTAR 2 rating: Moderate
Nguyen 2011 USA (77)	Systematic review and meta-analysis	**Stage:** unfavourable risk, non-metastatic **Treatment:** GnRHa	Pooled analysis of 8 RCTS n=4141 Control: no ADT	**CVM** Experimental group: incidence 11% (8.3-14.5); Control group: 11.2% RR 0.93 (7.9-1.10) no significant difference. Sub group analysis showed no association with CVM and ADT duration (≥3 years or ≤6 months)	AMSTAR 2 rating: Low
Scailteux 2016 France (80)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** CPT vs AA CAB vs GnRH agonist, CAB vs Orchiectomy, GnRH vs Orchiectomy, Orchiectomy vs Orchiectomy + AA, GnRH agonist vs GnRH antagonist, OT, Intermittent CAB vs continuous CAB, Orchiectomy vs AA,	Pooled analysis of 11 observational studies (n=193,620); 57 RCTs (n=31,037)	**MYOCARDIAL INFARCTION** **Observational**: RR(95% CI) Orchiectomy vs AA 2.04 (0.66, 8.33); GnRHa vs Orchiectomy 0.61 (0.30, 0.92); CAB vs OT 0.49 (0.19, 0.89); CAB vs GnRHa 0.97 (0.63, 1.47); GnRHa vs AA 1.43 (1.10, 1.85); CAB vs AA 1.34 (0.87, 2.06) **RCT:** CPT vs AA 0.49 (0.04, 5.39); GnRHant vs GnRHa 0.42 (0.23, 0.77) **STROKE** **Observational**: OT vs AA 1.14 (0.83, 1.56); GnRHa vs OT 1.00 (0.58, 1.72); CAB vs OT 0.71 (0.52, 0.97); CAB vs GnRHa 0.82 (0.66, 1.02); GnRHa vs AA 1.22 (0.93, 1.61); CAB vs AA 1.10 (1.02, 1.19) **RCT:** GnRHant vs GnRHa 0.42 (0.23, 0.77) 3.44 (0.22, 1.32)	AMSTAR 2 rating: High
Meng 2016 China (73)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** All ADT, GnRH alone, GnRH + AA, orchiectomy, AA alone	Pooled analysis 6 observational studies n=74,538 ADT users vs 85,947 non-ADT users **Control:** All ADT, GnRH alone, GnRH + antiandrogen, orchiectomy, AA alone	Incidence of stroke across all types of ADT (HR 1.12; 0.95-1.32) not significant; **Sub analyses:** GnRHa alone (HR 1.20; 1.12-1.28, p<0.001); GnRHa + AA (HR 1.23; 1.13-1.34, p<0.001); Orchiectomy (1.37; 1.33-1.46, p<0.001); AA alone (1.06; 0.71-1.57, p=0.078)	AMSTAR 2 rating: Moderate
Spratt 2018 USA (112)	Systematic review and meta-analysis	**Stage:** Recurrent **Treatment:** Salvage RT + GnRH	Pooled analysis of 2 RCTs: GETUG n=743, ADT duration GnRH agonist -6 months; RTOG n=760, ADT duration AA - 24 months **Control:** Salvage RT + AA	**Long term hypertension** (GnRHa) 12% vs (AA) 4% **Gynaecomastia** (GnRHa) 11% vs (AA) 70% **Vasomotor flushing** (GnRHa) 45% vs (AA) 1%	AMSTAR 2 rating: Low
Sciarra 2016 Italy (81)	Systematic review and meta-analysis	**Stage:** Advanced PCa **Treatment:** Degarelix	5 clinical trials n=1719 Pooled analysis where possible (1061 degarelix vs 658 GnRHa) **Control:** GnRH agonists	**Severe cardiovascular adverse effects** (3 trials) Deg 1.6%; GnRHa 3.6% (OR 0.55; 0.26-1.14, *P*>0.1) **Vasomotor flushing** Deg. 29%; GnRHa 27% (OR 1.06 95% CI 0.84-1.33, *P*=>0.1)	AMSTAR 2 rating: Low

			Follow-up duration heterogeneous but did not exceed 364 days	**erectile dysfunction** Deg. 9.5%; GnRHa 10% OR 0.94 (0.700-1.26, *P*=0.686)	
Rydzewska 2017 UK (79)	Systematic review and meta-analysis	**Stage:** Metastatic HSPCa **Treatment:** ADT + abiraterone acetate + prednisone/ prednisolone	Pooled analysis of 2 trials: LATITUDE n=597 & 602; STAMPEDE n = 500 + 502 **Control:** ADT alone	**CV events:** Grade III acute cardiac events Peto OR: 2.93 (1.74, 4.93, p<0.001); Grade III-IV vascular events 2.28 (1.71, 3.03, p<0.001) **hepatic disorder:** 3.09 (2.12, 4.50, p<0.001)	AMSTAR 2 rating: High
Iacovelli 2018 Italy (110)	Systematic review and meta-analysis	**Stage:** HSPCa & CRPCa **Treatment:** Abiraterone acetate & Enzalutamide	Pooled analysis of 7 Phase II & III clinical trials n=8660 Enzalutamide vs Placebo; Abiraterone acetate + prednisone vs placebo + prednisone; Enzalutamide vs bicalutamide Median treatment duration for experimental group: 8-24 months (control duration 3-14 months)	**CV events:** All grade 11.7% vs 8.6% RR 95% CI 1.36 (1.13-1.64, *p*=0.001); high grade 3.7% vs 2.0% RR 1.84 (1.21-2.80, *p*=0.004); **Abiraterone acetate:** all grade 13.7% & high grade 4.5% RR 1.41 (1.21-1.64 *p*<0.001) & 2.22 (1.60-3.07, *p*<0.001); **Enzalutamide:** all grade 8.6% & high grade 2.5% RR 1.25 (0.99-1.59 *p*=0.3) & 1.28 (0.45-3.66, *p*=0.7); comparison between abiraterone acetate & enzalutamide: no differences in RR. **HYPERTENSION:** All grade 19.6% vs 10.9% RR (95% CI) RR 1.98 (1.62-2.13, *p*=0.006); high grade 6.1% vs 3.1% RR 2.26 (1.84-2.77, *p*<0.001); **Abiraterone acetate:** all grade 26.2% & high grade 6.9% RR 1.79 (1.45-2.21, *p*<0.001) & RR 2.19 (1.73-2.78, *p*<0.001); **Enzalutamide:** all grade 10.5% & high grade 4.8% RR 2.66 (1.96-3.66 *p*<0.001) & RR 2.44 (1.64 - 3.63, *p*<0.001). Significant difference in RR for all grade, but not high-grade hypertension between Abiraterone acetate & Enzalutamide. **Sub analysis based on stage of PCa** HSPCa vs CRPaC for CV outcomes: **CRPCa** receiving Abiraterone acetate High-grade CV events (2.85% vs 6.45%, *P*<0.001). Same result for placebo (1.09% vs 3.43%, *P*<0.001). **HSPCa** receiving Abiraterone acetate Hypertension Higher incidence high & low grade events, but not significant. Abiraterone acetate compared to placebo: HSPCa High grade (4.6% vs 1.9%; *P*<0.001); all grade (1.9% vs 11.3%'=; *P*<0.001) Increased incidence of cardiac toxicity in patients treated for CRPCa related to longer duration of ADT.	AMSTAR 2 rating: Low
Roviello 2016 Italy (78)	Systematic review and meta-analysis	**Stage:** CRPCa **Treatment:** Abiraterone acetate + prednisone; Orteronel + prednisone (NA in Australia)	4 RCTs n=2849, 2067 control; 2 pre-chemotherapy, 2 post-chemotherapy **Control:** placebo + prednisone Median treatment duration: AA 8-13.8 months; Enzalutamide 11.7-16.6 months.	**Within trial incidence** Abiraterone acetate + prednisone vs control (**COU-AA-301** %all, %high; **COU-AA 302** %all, %high): **Hypertension** **301** 12 vs 8, 1 vs <1; **302** 24 vs 14, 5 vs 3 **Cardiac disorders** **301** 21 vs 15, 5 vs 3; **302** 302-23 vs 18; 8 vs 5. **Hepatotoxicity** **301** 15 vs 5; **302** 25 vs 8 **Across all studies**	AMSTAR 2 rating: Moderate

				<u>All grade AEs</u> relative risk (95% CI) **Hypertension**: RR 1.53 (1.30, 1.80, p<0.00001); **Cardiac disorders:** RR 1.47 (1.27, 1.70, p<0.00001); **Hepatotoxicity:** RR 1.93 (1.15, 3.24, p=0.001) **<u>High grade AEs</u> (≥ grade 3)** **Hypertension:** RR 1.36 (0.97, 1.92, p=0.08) **Cardiac disorders:** RR 1.55 (1.18, 2.05, p=0.02) **Hepatotoxicity:** RR 2.94 (0.95-9.08, p=0.06)	
Zhu 2018 China (85)	Systematic review and meta-analysis	**Stage:** Metastatic CRPCa **Treatment:** Enzalutamide, Abiraterone acetate	Pooled analysis 10 RCTs (5 Enzalutamide + 5 Abiraterone acetate) n=9520 **Control:** Placebo/ADT/ Prednisone/ Abiraterone + placebo /Bicalutamide	**Significant AE events** relative risk (95% CI) **<u>Abiraterone acetate</u>: all grade AEs** cardiac events RR 1.40, (1.22–1.62); hypertension (RR 1.70, 1.36–2.12); **High grade AEs (≥ grade 3)** cardiac events RR 1.93 (1.42–2.61), hypertension RR 2.16 (1.43–3.26) **<u>Enzalutamide</u>: all grade AEs** fatigue RR 1.29 (1.17–1.42); vasomotor flushing RR 1.94 (1.55-2.42); hypertension RR 2.62 (1.05–3.34); **High grade AES (≥ grade 3)** fatigue RR 1.50 (1.08-2.08) hypertension RR 2.66 (1.76–4.02) vasomotor flushing RR 1.94 (1.55–2.42)	AMSTAR 2 rating: Moderate
Gild 2018 US (113)	Population-based cohort study SEER-Medicare linked data	**Stage:** localised **Treatment:** GnRH agonists/antagonists	n=82,938 Age ≥66 years diagnosed 1992-2009 Median follow-up was 6.1 years (IQR 3.6 to 9.0) **Control:** non-ADT PCa	**Hepatotoxicity** hazard risk (95% CI) any liver disease HR 1.47 (1.35, 1.60), NAFLD HR 1.54 (1.40, 1.68), liver cirrhosis HR 1.35 (1.12, 1.60), and liver necrosis HR 1.41 (1.15, 1.72) Dose-response relationship observed between no. of ADT doses and NAFL and any liver disease Compared to no ADT, risk of NAFLD increased with no. of monthly equivalent doses of ADT: fewer than 7 vs more than 11 - HR 1.47 (1.31, 1.63) vs HR 1.72, (1.47, 2.02). Risk of any liver disease: fewer than 7 vs more than 11 - HR 1.40 (1.26, 1.55) vs HR 1.64 (1.43, 1.88)	NOS rating: Good
Guo 2018 China (66)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** GnRHa alone, GnRHa + AA, AA alone, orchiectomy	5 cohort studies n=170,851 ADT users & 256,704 non-ADT users n=170,851 ADT users & 256,704 non-ADT users **Control:** No ADT	**Thrombolytic embolisms** hazard risk (95%CI) **Deep Vein Thrombosis:** GnRH agonist alone HR 1.47 (1.07-2.03); GnRH agonist + AA HR 2.55 (2.1-2.94); AA alone HR 1.49(1.13- 1.96); orchiectomy HR 1.80 (0.93-3.47) not statistically significant differences. **Pulmonary embolism:** GnRH agonist alone HR 2.26 (1.78-2.26); orchiectomy HR 2.12 (1.44-3.11)	AMSTAR 2 rating: Low
Nead 2018 USA (74)	Systematic review and meta-analysis	**Stage:** locally advanced, advanced **Treatment:** Estrogens, GnRH + anti-androgen,	18 studies in pooled meta-analysis n=>250000 **Control (lesser exposed group):** no ADT, short-term ADT, intermittent ADT	relative risk (95% CI) ADT without estrogen RR 1.43 (1.78, 7.80, p<0.001) - 10 studies; estrogen only RR 3.72 (1.78-7.80, p<0.001) - 9 studies. Increased risk of	AMSTAR 2 rating: Moderate

		anti-androgen alone, orchiectomy		thromboembolic events ADT without estrogen for localised disease RR 1.10 (1.05-1.16, *p*=<0.001) ADT duration: >12 months ADT conferred statistically significant increased risk (RR 1.72 95% CI 1.30-2.28. p<0.001)	
Roviello 2018 Italy (120)	Systematic review and meta-analysis	**Stage:** Metastatic CRPCa **Treatment:** Enzalutamide, Abiraterone acetate + prednisone	11 studies n=11,751 Pooled analysis and sub analyses to address heterogeneity **Control:** placebo, bicalutamide	relative risk (95% CI) **Any grade of fatigue** ranged from 28-47% in experimental group & 8-44% in control group **Any grade fatigue** RR 1.27 (1.13-1.43); grade 3-4 fatigue RR 1.25 (0.92-1.71) **Sub analyses:** pre-chemotherapy fatigue statistically significant RR 1.47 (*P*=0.09); post chemotherapy no increase in RR; drug type no statistically significant difference in RR.	AMSTAR 2 rating: Moderate
Alibhai 2015 Canada (121)	Three-armed matched cohort study	**Stage:** Non-metastatic PCa **Treatment:** ADT any	n=87, median age 69.8 years 36-month follow-up **Controls:** PCa controls (no ADT) n=86, median age 69.8; healthy controls n=86, median age 67.8 (2004 – 2007)	Grip strength stable in control groups but declined sharply in ADT group by 3 months and remained stable to 36 months (P=.0041). TUG scores declined gradually in ADT group over 36 months; unchanged in control groups (P=.0008). Aggregate physical QOL declined in ADT users over time; remained stable in control groups (*P*=0.0001).	NOS rating: Good
Hussain 2010 Canada (123)	Matched cohort study using linked administration data	**Stage:** Non-metastatic PCa **Treatment:** LHRH agonists, non- steroidal or steroidal anti-androgens alone or in combination & orchiectomy	n=87, median age 69.8 years 12-month follow-up **Controls:** PCa controls (no ADT) n=86, median age 69.8; healthy controls n=86, median age 67.8 (2004 – 2007)	35% of ADT users sustained falls over 12 months prospective follow up vs 18.1% PCa controls & 21.7% healthy controls (*P*=0.08)	NOS rating: Good
Kunath 2015 Germany (70)	Systematic review and meta-analysis	**Stage:** Advanced HSPCa **Treatment:** Non- steroidal anti-androgen monotherapy	Pooled analysis of studies reporting adverse events: Gynaecomastia 9 studies n = 2774; Mastalgia 8 studies n=2670; Vasomotor Flashing 9 studies n = 2774 **Control:** LHRH agonists or orchiectomy	relative risk (95% CI) Non-steroidal AA Significantly higher rates of occurrence for: Mastalgia RR 22.97 (14.79-35.67); Gynaecomastia RR 8.43 (3.19-22.28) Significantly decreased rates of occurrence for: Vasomotor flashing: RR 0.23 (0.10-0.27)	AMSTAR 2 rating: High
Daly (2012) Ireland (115)	RCT (ICORG 97-01)	**Stage:** Localised PCa **Treatment:** Neoadjuvant ADT (NADT) & Radiotherapy (RT) 4 months (n=109)	n=276 eligible patients (Feb. 1997-Dec. 2001) Median age 67 years Median follow-up 80 months **Control:** Neoadjuvant ADT (NADT) & Radiotherapy (RT) 8 months (n=121)	No significant difference between 4-month & 8-month NADT arms (48% vs 61% decrease in sexual potency) 26% men can expect to retain sexual function at 5 years	ROB 2 rating: Some concerns
Jones (2011) USA (116)	RCT Radiation Therapy Oncology Group (RTOG)	**Stage:** Localised PCa **Treatment:** 4 months Neoadjuvant ADT (NADT) & Radiotherapy (RT) (n=987)	n=1979 eligible patients (1994-2001) **Experimental:** RT + ADT (n=987) Median age 70 years (47-91) **Control:** RT alone (n=992) Median age 71 years (47-88) Median follow-up 9.1 years	potency rate ADT + RT: Baseline 48%; 1 year 21% RT alone: Baseline 54%; 1 year 31% (*P*=0.004)	ROB 2 rating: High
Nead 2017 USA (76)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** Primary ADT, anti-	**Pooled analysis** 168,756 total population	relative risk (95% CI) Depression RR 1.41 (1.18, 1.70; p<0.001);	AMSTAR 2 rating: Moderate

		androgen, RT/RP + ADT, orchiectomy	**Primary** 18 studies meta-analysed (n=77,017 ADT users); **Sub analyses** Prospective (6 studies), Retrospective (11 studies), cross sectional (1 study) **Control:** lesser exposed comparison group (any ADT vs no ADT, short term ADT, intermittent ADT)	**Sub analyses** **Localised PCa** RR 1.85 (1.20, 2.85; *P*=0.005) **Studies using clinical diagnosis of depression RR** 1.19 (1.08, 1.32, *P*=0.001) No statistically significant differences between **IADT & CADT** RR 1.00 (0.50, 1.99; *P*=0.992)	
Sun 2018 USA (82)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** Primary ADT, anti-androgen, RT/RP + ADT, orchiectomy	Pooled analysis in two sub groups – prospective and retrospective. High heterogeneity 6 cohort studies n=68,086 (2 prospective; 4 retrospective) **Control:** No ADT	Odds ratio (95% CI) **Prospective:** Cognitive impairment definition-1.5 or more SDs below norms on 2+ tests: OR 1.56 (0.50, 4.91, *p*=0.441). Cognitive impairment definition-2 or more SDs below norms on 2+ tests: OR 1.75 (0.49, 6.25, *p*=0.389). **Retrospective:** OR 1.28 (0.93, 1.76, *p*=0.130)	AMSTAR 2 rating: Low
Nead 2017 USA (75)	Systematic review and meta-analysis	**Stage:** Any ADT, any LHRHa, continuous LHRHa +AA **Treatment:** ADT & dementia risk vs a lesser exposed comparison group (no ADT, short term ADT, intermittent ADT)	9 cohort studies n=50,541 **Primary analysis** **1.** 6 studies - risk of dementia from ADT; **Sub analyses** **2.** 5 studies - risk of all cause dementia; **3.** 3 studies - Alzheimer's disease **Control**: No ADT, intermittent LHRHa + AA	**Dementia** hazard ratio (95% CI) 1. HR 1.47 (1.08-2.00) 2. HR 1.46 (1.05-2.02) 3. HR 1.25 (0.99-1.57)	AMSTAR 2 rating: Moderate
McGinty 2014 USA (72)	Systematic review and meta-analysis	**Stage:** Any **Treatment:** GnRH agonists, short- & long-term ADT, active surveillance	Pooled meta-analysis across all study designs Mean ADT duration: 23 -31 months (cross-sectional studies; n=3) ADT duration 1-9 months after ADT initiation (longitudinal studies; n=11)	Weighted average effect (95% CI) visuomotor skills -0.67 (-1.17, -0.17; *P*=0.008) Meta-regression indicated that time on ADT was significantly associated with effect of ADT on visuomotor ability (*P*=0.04).	AMSTAR 2 rating: Low

Key: BMI body mass index; BMD bone mineral density; RCT randomised controlled trial; LHRH luteinising hormone replacing hormone; GnRH gonadotrophin releasing hormone; AA anti-androgen; RT radiotherapy; RP radical prostatectomy; M0 non-metastatic; M1 metastatic; IADT intermittent androgen deprivation therapy; CADT continuous androgen deprivation therapy; HSPCa hormone sensitive prostate cancer; CRPCa castrate resistant prostate cancer; mCRPCa metastatic castrate resistant prostate cancer; MI myocardial infarction; IHD ischaemic heart disease; CV cardiovascular; CVD cardiovascular disease; CVM cardiovascular mortality; TUG timed up & go; aHR adjusted hazard ratio; HR hazard ratio; RR relative risk; OR odds ratio; SD standard deviation; AMSTAR 2 tool for assessing the methodological quality of systematic reviews version 2; ROB 2 risk of bias instrument version 2; NOS Newcastle Ottawa Scale to assess quality of observational studies.

Appendix 3 Quality assessment tools (Chapter 2)

AMSTAR 2 Critical appraisal tool for systematic reviews

AMSTAR 2	1	2	3	4	5	6	7	8	9i	9ii	10	11i	11ii	12	13	14	15	16	RESULT
Systematic Review First author, year	PICO Y/N	Protocol Partial Y/Y/No	Choice of study designs Y/N	Comp. literature search Partial Y/Y/N	Duplicate study selection & consensus Y/N	Duplicate data extraction Y/N	Exclusions list with reasons PY/Y/N	Adequate study detail PY/Y/N	Satisfactory RoB -**RCTs** PY/Y/N/only NRSI	Satisfactory RoB -**NRSI** PY/Y/N/ only RCTs	Sources of funding reported for included studies Y/N	Appropriate meta-analysis **RCTs** Y/N No meta-analysis	Appropriate meta-analysis **NRSI** Y/N No meta-analysis	Impact of RoB on results of evidence synthesis Y/N/No meta-analysis	Individual study RoB accounted for in results of review Y/N	Heterogeneity addressed Y/N	Impact of publication bias on results of review Y/N/No meta-analysis	Sources of conflict reported Y/N	Confidence in overall results of review rating
Haseen 2010	Y	N	N	Y	Y	Y	PY	Y	N	N	N	N	N	N	N	PY	Y	N	low
Kim 2019	Y	Y	N	Y	Y	Y	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	N	Y	low
Bosco 2015a	Y	PY	Y	Y	N	N	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	N	Y	low
Wang 2016	Y	PY	N	Y	Y	Y	Y	Y	NRSI	Y	Y	NRSI	Y	Y	Y	Y	Y	Y	high
Bosco 2015	Y	N	Y	Y	N	Y	PY	Y	NRSI	Y	Y	NRSI	Y	Y	Y	Y	Y	Y	mod
Jin 2016	Y	PY	N	Y	N	Y	N	PY	Y	RCT	N	Y	RCT	Y	Y	Y	Y	Y	mod
Magnan 2015	Y	PY	N	Y	Y	Y	PY	Y	Y	RCT	N	Y	RCT	Y	Y	N	Y	Y	mod
Zhao 2014	Y	PY	Y	Y	N	Y	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	Y	Y	mod
Nguyen 2011	Y	N	N	PY	N	Y	N	Y	Y	RCT	N	Y	RCT	N	N	Y	Y	Y	low
Scailteux 2016	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	high
Meng 2016	Y	PY	N	PY	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	mod
Spratt 2018	Y	N	N	PY	Y	Y	N	Y	N	RCT	N	No Met	RCT	N	N	N	No Met	Y	low
Sciarra 2016	Y	N	Y	PY	Y	Y	N	Y	N	RCT	N	Y	RCT	N	N	Y	N	Y	low
Rydzewska 2017	Y	Y	Y	Y	Y	Y	N	Y	Y	RCT	N	Y	RCT	Y	Y	Y	Y	Y	high

Iacovelli 2018	N	Y	N	Y	Y	Y	PY	Y	Y	RCT	N	Y	RCT	N	N	N	N	Y	low
Roviello 2016	Y	Y	Y	Y	Y	Y	N	PY	Y	RCT	N	Y	RCT	N	Y	Y	N	Y	mod
Zhu 2018	Y	PY	N	Y	Y	Y	PY	Y	Y	RCT	N	Y	RCT	N	Y	Y	Y	Y	mod
Guo 2018	Y	PY	N	Y	N	Y	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	N	Y	low
Nead 2018	Y	PY	Y	Y	Y	Y	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	Y	Y	mod
Roviello 2018	Y	PY	Y	Y	N	N	N	PY	Y	RCT	N	Y	RCT	N	Y	Y	N	Y	mod
Kunath 2015	Y	PY	Y	Y	Y	Y	N	Y	Y	RCT	N	Y	RCT	Y	Y	Y	Y	Y	high
Nead 2017	Y	PY	N	Y	Y	Y	Y	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	Y	Y	mod
Sun 2018	Y	Y	Y	Y	Y	Y	PY	Y	NRSI	PY	N	NRSI	Y	Y	Y	Y	N	Y	low
Nead 2017a	Y	PY	N	Y	Y	Y	PY	Y	NRSI	Y	N	NRSI	Y	Y	Y	Y	Y	Y	mod
McGinty 2014	Y	PY	Y	Y	Y	Y	PY	Y	NRSI	N	N	NRSI	Y	Y	Y	Y	Y	Y	low

Abbreviations: Y yes, PY; partial yes; N no; RCT randomised controlled trial; NRSI non-randomised study of intervention; Met meta-analysis

Risk of Bias (ROB 2) tool for RCTs

Risk of Bias Domain First Author Year	Randomisation process	Deviations from intended intervention (effect of adhering to intervention)	Missing outcome data	Measurement of outcome	Selection of reported result	Risk of Bias judgement
Daly 2012	High	Low	Low	Low	Low	Low - However some concerns regarding conflicts of interest on the part of some authors with pharmaceutical companies
Graff 2016	Low	Low	Low	Low	Low	Low - However, some regarding authors who have conflicts of interest with pharmaceutical companies in the form of funding, honorariums, consultancy, employment, speaker fees, etc.
Jones 2011	Low	High	Low	High	Low	High – two authors had conflicts of interest with pharmaceutical companies as advisors, recipients of speaking fees, etc.
Smith 2018	Low	Low	Low	Low	Low	Low - However potential conflicts of interest for a number of authors with pharmaceutical companies (employees, recipients of funding, honorariums, travel grants, etc.)

Newcastle-Ottawa Scale for Cohort Studies

First Author year	**Selection -1** Representativeness exposed cohort (maximum 1 star)	**Selection -2** Non-exposed cohort (maximum 1 star)	**Selection -3** Ascertainment of exposure (maximum 1 star)	**Selection - 4** Outcome of interest not present at start of study (maximum 1 star)	**Comparability** cohorts by design or control for confounders (Maximum 2 stars based on factors controlled for)	**Outcome -1** Assessment (maximum 1 star)	**Outcome - 2** Length of follow-up (maximum 1 star)	**Outcome - 3** Adequacy of follow-up (maximum 1 star)	**Score** (Good, Fair, Poor)
Ng 2018	*	*	*	*	*	*	*	*	Good
Shao 2013	*	*	*	*	**	*	*	*	Good
Alibhai 2010	*	*	*	*	**	*	*	*	Good
Wallis 2016	*	*	*	*	**	*	*	*	Good
Sun 2016	*	*	*	*	**	*	*	*	Good
Beebe-Dimmer 2012	*	*	*	*	**	*	*	*	Good
Tsai 2017	*	*	*	*	**	*	*	*	Good
Gild 2018	*	*	*	*	**	*	*	*	Good
Alibhai 2015	*	*	*	*	**	*	*		Good
Hussain 2010	*	*	*	*	*	*	*		Good

Appendix 4: Sensitivity and scenario analyses (Chapter 6)

Test to be modelled	Detailed assumptions	Justification
Sensitivity analyses (SA)		
SA1: Variation in the magnitude of effect size using the upper and lower confidence interval limits	Assumes benefit of the intervention varies between the calculated confidence interval of the effect size in all outcome measures.	Plausible variation in effect size.
SA2: Societal perspective based on patient out-of-pocket costs	In order to participate in the exercise intervention, participants would need to access an exercise facility and thus have a membership. They would also need to travel to exercise facility. No productivity losses included due to mean age of population (72 years); only seven participants in sample engaged in employment - 4 part time & 3 full time).	Plausible costs incurred by participants. Societal perspective not included as a base case due to lack of data regarding societal benefits.
SA3: Variation in the intervention cost/ number of participants	Variation in number of participants attending one session – more people reduces cost	Plausible variation in cost when more participants can attend one session
SA4: Maintenance of HRQoL outcomes after the 6-month home-based exercise program	Maintenance of benefit beyond the supervised intervention based on evidence in the literature[1].	Plausible maintenance of HRQoL based on follow-up data after 6-month home-based intervention immediately following 6-month supervised program.
Scenario analyses (S) (healthcare perspective)		
S1 Scalability of intervention	MBS AEP item numbers and admin staff wages used to scale to a community-based intervention; increasing participants per session and reducing implementation costs.	Plausible variation in cost, particularly if run as a community/clinical intervention, with set time frames.
S2 Private cancer clinic located in multiple locations provide access to exercise clinic & AEP.	Use of in-house exercise clinic included as part of the business model (Team care arrangements provided as part of Chronic Disease Management Plan [CDMP] – 1 GP, 1 consulting physician + allied health practitioners [AEP](MBS item 10953)) (MBS items 721 & 723). Exercise equipment & maintenance included as opportunity cost in payment to cancer clinic as part of patient fees.	Potential alternative model of care. Cost reallocation that impacts on uptake & attendance, improving impact & reducing overheads. Patients more likely to attend if little perceivable added cost burden, co-located with oncology services, quieter, more personal space shared with people in similar circumstances[2,3]. Private cancer clinics are currently operating using this model, where exercise clinic costs are absorbed as part of a business model designed to improve market share.

Abbreviations: SA sensitivity analysis; S scenario analysis; GP general practitioner; MBS Medicare benefits schedule; PCa prostate cancer; AEP accredited exercise physiologist; CDMP chronic disease management plan

Notes: [1]Henderson, RM, Miller, ME, Fielding, RA, Gill, TM, Glynn, NW et al. Maintenance of physical function 1 year after exercise intervention in at-risk older adults: Follow-up from the LIFE study. Journals of Gerontology: Medical Sciences. 2018, 73(5):688-95.

[2]Cormie P, Oliffe JL, Wootten AC, Galvão DA, Newton RU, Chambers SK. Improving psychosocial health in men with prostate cancer through an intervention that reinforces masculine values – exercise. Psycho-Oncology. 2016; 25:232-5.

[3]Cormie P, Turner B, Kaczmarek E, Drake D, Chambers SK. A qualitative exploration of the experience of men with prostate cancer involved in supervised exercise programs. Oncol Nurs Forum. 2015;42(1):24-32.

Appendix 5 Supplementary Information (Chapter 7)

Supplementary file 1 Cost of exercise intervention (AU$2019)

Intervention cost component	Cost description	Unit of measure	Cost per participant
GP consent	MBS Item 23: Level B GP consultation lasting less than 20 minutes (2019)	1 consultation ($38.20)	$38
Registration of intervention participants & administration	Clerks private sector award 2010 level 3 $911/week ($23.97/hour) + 20% on costs (2019)	30 mins clerk time + phone calls	$15
AEP pre-program consultation	MBS Item no. 81115	1 consultation	$81
Subtotal			**$134**
50-week exercise intervention	1-hour exercise session AEP MBS Item no. 10932	Up to 10 participants per session	$633
Total per participant (healthcare perspective)			**$767**

Abbreviations: GP general practitioner; MBS Medicare benefits schedule; RCT randomised controlled trial; AEP accredited exercise physiologist

Supplementary file 2 Univariate sensitivity analysis

Variable	Strategy	Cost	Effectiveness (QALYs)	ICER	NMB	C/E
Base C_exercise $767 Base - 12mos AEP (MBS no. 10953)-health service	Exercise intervention (10 persons)	$2,952	2.10	Cost saving	$102,112	1.40K
SA1a C_exercise $1917 Base - 12mos AEP (MBS no. 10953)-part societal	Exercise intervention (10 persons) + OOP costs	$4,102	2.10	Cost saving	$100,962	1.95K
SA2 C_exercise $1188 - 12mos AEP (MBS no. 10953)-health service	Exercise intervention (6 persons)	$3,373	2.10	Cost saving	$101,691	1.61K
SA2a C_exercise $2338 - 12mos AEP (MBS no. 10953)-part societal	Exercise intervention (6 persons) + OOP costs	$4,523	2.10	10.61K	$99,101	2.00K
SA3 C_exercise $450 6mos AEP (MBS no. 10953) + 6mos home-based-health service	Exercise intervention 6mos + 6mos home-based (10 persons)	$2,635	2.10	Cost saving	$102,429	1.25K
SA3a C_exercise $709 - 6mos AEP (MBS no. 10953) + 6mos home-based-part societal	Exercise intervention 6mos + 6mos + OOP costs (10 persons)	$2,894	2.10	Cost saving	$101,691	1.38K
SA4 C_exercise $2154 12mos AEP group diabetes (MBS no. 81110)-health service	Exercise intervention diabetes (10 persons)	$4,339	2.10	5.58K	$100,725	2.06K
SA4a C_exercise $3304 12mos AEP group diabetes (MBS no. 81110)-part societal	Exercise intervention diabetes +	$5,489	2.10	37.05K	$99,575	2.61K

	OOP costs (10 persons)					
SA5 C_majfracture Mean -50% +50% ($10K-$30K)	Exercise intervention (10 persons)	$2,631 $3,230	2.10	Cost saving	$102,433 $101,834	1.25K 1.54K
SA6-C_mininjury Mean -50% +50% ($0.55K-$1.65K)	Exercise intervention (10 persons)	$2,470 $3,409	2.10	Cost saving	$102,594 $101,655	1.18K 1.62K
SA7 P_Risk_Fall_Reduction Mean -0.2 +0.2 (RR 0.56-0.96)	Exercise intervention (10 persons)	$2,338 $3,571	2.11 2.09	Cost saving	$103,391 $100,896	1.11K 1.71K
SA8 P_Risk_Fracture_Reduction Mean -0.2 +0.2 (RR 0.24-0.64)	Exercise intervention (10 persons)	$2,630 $3,274	2.10	Cost saving	$102,504 $101,720	1.25K 1.56K
SA9 P_firstfall Mean -/+50% (0.0525-0.1575)	Exercise intervention (10 persons)	$2,031 $3,615	2.13 2.08	Cost saving	$104,271 $100,552	0.96K 1.74K
SA10 P_recurfall Mean -/+50% (0.1145-0.3435)	Exercise intervention (10 persons)	$2,530 $3,326	2.10 2.08	Cost saving	$102,692 $101,600	1.20K 1.58K
SA11-P_fracture Mean -/+50% (0.06-0.18)	Exercise intervention (10 persons)	$2,608 $3,337	2.10	Cost saving	$102,530 $101,643	1.24K 1.59K
SA12 U_atriskfall Mean -0.1 QALY +0.1 QALY (0.69-0.89)	Exercise intervention (10 persons)	$2952	1.93 2.28	Cost saving	$ 93,329 $110,894	1.53K 1.30K
SA13 StartingAge Mean -8 yrs +8 yrs (60-76)	Exercise intervention (10 persons)	$2976 $2911	2.12 2.06	Cost saving	$103,145 $100,335	1.40K 1.41K
SA14 Time horizon (total cycles) 6 yrs (24)	Exercise intervention (10 persons)	$5600	3.78	Cost saving	$183,647	1.48K

Abbreviations: QALYs quality adjusted life years ICER incremental cost-effectiveness ratio NMB net monetary benefit C/E cost divided by effect SA-C sensitivity analysis cost SA-P sensitivity analysis probability SA-U sensitivity analysis utility yrs years

Appendix 6 Co-authored publications

Chapter 2 Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review

Copyright statement and statement of contribution to co-authored published paper

This chapter includes a co-authored paper.

Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-05255-5

REVIEW ARTICLE

Check for updates

Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review

Kim Edmunds[1,2] · Haitham Tuffaha[1,2] · Daniel A Galvão[3] · Paul Scuffham[1,2] · Robert U Newton[3]

Received: 1 September 2019 / Accepted: 18 December 2019

Abstract

Purpose Androgen deprivation therapy (ADT) has broad application in the treatment of prostate cancer (PC) and is associated with numerous, debilitating adverse effects. Increasing use of ADT for PC, longer timeframe for treatment (increased uptake of PSA testing and earlier diagnosis), as well as improved survival and an ageing population, means patients can live for a considerable period of time on or after ADT, experiencing these adverse effects. A number of systematic reviews of adverse effects of ADT for PC exist; however, no single systematic review has previously examined the evidence for all adverse effects, including newer forms of ADT.

Methods A systematic review of existing systematic reviews of ADT for PC was conducted (2010–February 2019), as per Cochrane guidelines, to identify the highest level of risk/incidence evidence available, supplemented by evidence drawn from individual studies where no systematic review existed.

Results Incidence data was generated for 19 adverse effect subgroups, classified according to the common terminology criteria for adverse events (CTCAE).

Conclusion Incidence of adverse effects provides valuable information for future burden of disease studies. This information can better guide clinical management to reduce symptoms for patients and assist patients to make more informed decisions about their treatment, potentially improving disease outcomes. It also highlights the importance of supportive care for PC patients receiving ADT and their carers. For analysts conducting economic evaluations, the inclusion of adverse effects in PC decision analytic models can provide more comprehensive and accurate information for decision makers.

Keywords Prostate cancer · Androgen deprivation therapy · Adverse effects · Incidence

Introduction

Since the advent of PSA testing in the 1990s, the rising incidence and burden of prostate cancer (PC) has been a cause for concern. Treatment options for men with PC are varied and depend on a number of factors such as expected survival, risk of progression, stage and grade of cancer at diagnosis, age and health of the patient, family history, personal preferences of the patient and adverse effects of treatment. Androgen deprivation therapy (ADT) suppresses the production of androgen, which fuels the growth of PC. It has broad application in the treatment of PC, and many types of ADT are currently in use in Australia (Table 1). ADT is predominantly used for intermediate or higher risk disease as well as advanced and metastatic cancer. It is also maintained when cancer becomes castration resistant. In addition, it is used as neo-adjuvant, concurrent, and adjuvant therapy with prostatectomy and radiotherapy [1–4].

ADT for PC is associated with numerous and often debilitating adverse effects. The National Institute of Cancer defines an adverse effect as: "an unexpected medical problem that happens during treatment with a drug or other therapy.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-019-05255-5) contains supplementary material, which is available to authorized users.

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Statement of contribution to co-authored paper

I, Kim Edmunds, contributed to the original idea of the paper, designed the search strategy, reviewed the literature and wrote the manuscript for the publication:

Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU. Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Journal of Supportive Care in Cancer. 2020.

(Signed) (Date) November 22, 2020
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Chapter 3 The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer

Copyright statement and statement of contribution to co-authored published paper

This chapter includes a co-authored paper.

Supportive Care in Cancer
https://doi.org/10.1007/s00520-020-05637-0

REVIEW ARTICLE

The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review

Kim Edmunds[1,2] · Haitham Tuffaha[3] · Paul Scuffham[1,2] · Daniel A Galvão[4] · Robert U Newton[4,5]

Received: 7 March 2020 / Accepted: 16 July 2020

Abstract

Purpose Prostate cancer (PCa) is the most commonly diagnosed cancer in Australia, accounting for one quarter of all new cancer diagnoses for males. Androgen deprivation therapy (ADT) is the standard first-line therapy for metastatic PCa but is also used across much of the spectrum of disease. Unfortunately, debilitating adverse effects are a significant and largely unavoidable feature of ADT. A recent systematic review of adverse effects of ADT identified 19 sub-groups classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The potential for multiple simultaneous adverse effects, their associated management and the impact of adverse effects on cancer outcomes and quality of life are important considerations in the treatment and supportive care of men with PCa. Exercise is increasingly being recognized as an efficacious strategy in managing these adverse effects.

Methods A rapid review was undertaken to examine the role of exercise in the management of the most commonly reported ADT adverse effects classified according to the CTCAE sub-groups. A systematic search was conducted in Medline, PsycINFO, Google Scholar and Google for the years 2010 to September 2019 to identify the benefits of exercise in managing the adverse effects of ADT for PCa.

Results There is strong evidence for exercise as medicine in addressing several of the adverse effects of PCa such as loss of muscle mass and strength, fatigue and declining physical function. Moderate level evidence for PCa exists for exercise-induced improvements in depression and anxiety, bone loss, and sexual dysfunction. While evidence of the effectiveness of exercise is lacking for many adverse effects of ADT for PCa, evidence in the cancer population as a whole or other clinical populations is strong, and many clinical guidelines recommend exercise as a fundamental part of their clinical management. With the exception of gynaecomastia and breast pain, there is increasing evidence (PCa, cancer or other clinical populations) to suggest that exercise has the potential to reduce and even prevent many of the adverse effects of ADT, thus improving survivorship outcomes for men with PCa.

Conclusion Exercise has the potential to reduce and even prevent many of the adverse effects of ADT, thus improving survivorship outcomes for men with PCa. The use of exercise for PCa management has the potential to translate into health and economic benefits in improved quality of life and fewer complications, resulting in savings to the health care system, enhanced productivity and reduced patient and carer burden. Exercise thus has the potential to improve quality of life for this population as well as generate significant cost savings.

Keywords Prostate cancer · Androgen deprivation therapy · Adverse effects · Management · Exercise medicine

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Published online: 22 July 2020

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Statement of contribution to co-authored paper

I, Kim Edmunds, contributed to the original idea of the paper, designed the search strategy, reviewed the literature and wrote the manuscript for the publication:

Edmunds K, Tuffaha H, Galvão DA, Scuffham P, Newton RU. The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer. Journal of Supportive Care in Cancer. 2020.

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Chapter 5 Demonstrating the value of early economic evaluation alongside clinical trials: exercise medicine for men with metastatic prostate cancer

Copyright statement and statement of contribution to co-authored published paper

This chapter includes a co-authored paper (under review).

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Statement of contribution to co-authored paper

I, Kim Edmunds, contributed to the original idea of the paper and the design of the economic analysis, conducted the analysis and wrote the manuscript for the publication:

Edmunds K, Scuffham P, Reeves P, Galvão DA, Taaffe DR, Newton RU, Spry N, Joseph D, Tuffaha H. Demonstrating the value of early economic evaluation alongside clinical trials: exercise intervention for men with metastatic prostate cancer.

(Signed) _____(Date) 22 Nov 2020___
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Chapter 6 Cost-effectiveness analysis of supervised exercise training men with prostate cancer previously treated with radiation therapy and androgen deprivation therapy

Copyright statement and statement of contribution to co-authored published paper

This chapter includes a co-authored paper.

Applied Health Economics and Health Policy
https://doi.org/10.1007/s40258 020 00564 x

ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Supervised Exercise Training in Men with Prostate Cancer Previously Treated with Radiation Therapy and Androgen-Deprivation Therapy

Kim Edmunds[1,2] · Penny Reeves[3,4] · Paul Scuffham[1,2] · Daniel A. Galvão[5,6] · Robert U. Newton[5,6] · Mark Jones[3] · Nigel Spry[5,7,8] · Dennis R. Taaffe[5,6] · David Joseph[5,7,9,10,11] · Suzanne K. Chambers[12] · Haitham Tuffaha[1,2]

Abstract

Background Exercise for prostate cancer (PCa) survivors has been shown to be effective in addressing metabolic function and associated co-morbidities, as well as sarcopenia and significant functional impairment resulting from long-term androgen deprivation. Evidence on the cost-effectiveness of exercise interventions for PCa, however, is lacking, thus the aim of this study was to determine the cost-effectiveness of a supervised exercise intervention for long-term PCa survivors who previously received radiation therapy and androgen-deprivation therapy.

Methods Cost-effectiveness analysis from an Australian healthcare-payer perspective was conducted using patient-level data from a multicentre randomised controlled trial (RCT) of supervised exercise training (resistance and aerobic) compared to receiving printed exercise material and a recommendation to exercise in long-term PCa survivors (> 5 years post-diagnosis). Analysis was undertaken for the 6-month supervised exercise portion of the intervention, which involved 100 men aged between 62 and 85 years, 50 in each arm. The primary outcome was cost per quality-adjusted life-years (QALYs).

Results A 6-month supervised exercise intervention for PCa survivors resulted in an incremental cost-effectiveness ratio of AU$64,235 (2018 AUD) at an incremental cost of AU$546 per person and a QALY gain of 0.0085. At a willingness-to-pay of AU$50,000, the probability that the intervention is cost-effective was 41%. Sensitivity analysis showed that maintenance of benefits via a 6-month home-based intervention, immediately following the supervised intervention, lowered the cost per QALY gained to AU$32,051.

Discussion This is the first cost-effectiveness analysis of exercise for PCa survivors. The intervention was effective, but unlikely to be cost-effective at the generally accepted willingness-to-pay of AU$50,000 per QALY. It is likely that evidence to support cost savings from post-intervention outcomes would reveal greater benefits and contribute to a more comprehensive cost-effectiveness analysis. Future RCTs should incorporate longer follow-up durations and collection of data to support modelling to capture future health benefits. Measures of quality of life or utility more sensitive to the impact of physical activity would also improve future economic evaluations.

1 Introduction

Prostate cancer (PCa) is a significant public health issue. It has a high incidence and is the cause of significant morbidity and mortality. In Australian men, it is the most commonly diagnosed cancer and the second most common cause of cancer death after lung cancer [1]. PCa needs testosterone, an androgen (male sex hormone), to grow. Androgen-deprivation therapy (ADT), which reduces or blocks androgen production, is thus widely used across the spectrum of PCa from high-risk localised disease to metastatic disease. However, it is associated with potentially debilitating adverse effects such as changes in body composition [e.g., increased fat mass, reduced muscle mass (sarcopenia)], metabolic complications and decline in physical function. The risk of adverse effects is an important consideration for men with long life expectancies, such as those men receiving

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40258-020-00564-x) contains supplementary material, which is available to authorized users.

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Published online: 28 February 2020

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Statement of contribution to co-authored paper

I, Kim Edmunds, contributed to the original idea of the paper and the design of the economic analysis, conducted the analysis and wrote the manuscript for the publication:

Edmunds K, Reeves P, Scuffham P, Galvão DA, Newton RU, Jones M, Spry N, Taaffe DR, Joseph D, Chambers S, Tuffaha H. Cost-effectiveness analysis of supervised exercise training men with prostate cancer previously treated with radiation therapy and androgen deprivation therapy. Applied Health Economics and Health Policy.

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Chapter 7 Exercise in preventing falls and fractures for men with prostate cancer receiving androgen deprivation therapy: a modelled cost-utility analysis

Copyright statement and statement of contribution to co-authored published paper

This chapter includes a co-authored paper (under review).

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Edmunds K, Scuffham P, Galvão DA, Newton RU, Tuffaha H. A modelled cost-effectiveness analysis of exercise in preventing falls and fractures for men with localised prostate cancer. Applied Health Economics and Health Policy.

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