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

Cost-effectiveness analysis of exercise for prostate cancer survivors

Kim Edmunds^{1,2*} ORCID 0000-0001-7379-1294

Penny Reeves^{3,4}

Paul Scuffham^{1,2} ORCID 0000-0001-5931-642X

Daniel A Galvão^{5,6} ORCID 0000-0002-8209-2281

Robert U Newton^{5,6}

Mark Jones³ ORCID 0000-0003-1736-1702

Nigel Spry^{5,7,8} ORCID 0000-0001-8659-5065

Dennis R Taaffe^{5,6}

David Joseph^{5,7,9,10,11}

Suzanne K Chambers¹² ORCID 0000-0003-2369-6111

Haitham Tuffaha^{1,2} ORCID 0000-0003-2993-3480

¹Centre for Applied Health Economics, Griffith University, Nathan, QLD

²Menzies Health Institute, Queensland

³Hunter Medical Research Institute, New Lambton Heights, NSW

⁴School of Medicine and Public Health, University of Newcastle, Callaghan, NSW

⁵Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA

⁶School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA

⁷Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, WA

⁸GenesisCare, Joondalup, WA

⁹Faculty of Medicine, University of Western Australia, Nedlands, WA

¹⁰GenesisCare, Wembley, WA

¹¹5D Clinics, Claremont, WA

¹²Faculty of Health, University of Technology, Sydney, NSW

Corresponding author*

E k.edmunds@griffith.edu.au

T 61737359112

Abstract

Introduction

Exercise for prostate cancer (PCa) survivors has been shown to be effective in addressing metabolic function and associated comorbidities, 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 multi-centre randomised controlled trial 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 per cent. 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 \$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.

Key Points for Decision Makers

Based on currently available evidence, there was a 41% probability that the 6-month supervised exercise intervention would be cost effective at a willingness-to-pay of AU\$50,000 per QALY.

A home-based exercise program conducted for six months immediately following the supervised training program has the potential to maintain benefits gained, possibly providing a cost effective policy option to mitigate the side effects of ADT for PCa survivors.

Future RCTs should be designed to incorporate longer follow-up and approaches that better capture the benefits of exercise to improve economic evaluations.

Acknowledgements

We would like to acknowledge the contribution of Jim Denham, Director of the RADAR trial, who, alongside Daniel Galvão, arranged the exercise substudy. Kim Edmunds would like to express her appreciation for the interest Jim Denham took in her PhD project; he generously shared his expertise in relation to the RADAR trial, the adverse effects of ADT and their impact on PCa patients. This was invaluable information early in the PhD process.

Kim Edmunds' PhD research was supported by an Australian Postgraduate Award scholarship and an Inspiring Minds scholarship from Edith Cowan University.

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 neoadjuvant or adjuvant therapy with curative radiation[2]. In older PCa survivors (>70 years), testosterone does not always recover, so adverse effects for this population may not be temporary[2].

Exercise has been shown to be effective in addressing metabolic function and associated comorbidities (e.g. diabetes, cardiovascular disease, etc.), as well as sarcopenia and significant functional impairment resulting from long term androgen deprivation[3-12, 2]. 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[5]. 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[9]. 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[13]. 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[14-21]. Eight studies were identified in the literature, six related to breast cancer[20, 21, 15, 17-19], one to lung cancer[14] and another to a number of different cancers (breast, colon, ovarian, cervical, testicular and lymphoma)[16]. Mode of delivery of exercise interventions differed across studies, from the use of a DVD in the home with no supervision[15]; delivery by physiotherapists[21, 16-19]; or face-to-face or telephone delivery by qualified exercise physiologists (EPs) [20, 21]. 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[1]. 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[2].

2 Methods

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[2]. The comparator arm represents usual care; healthcare providers should recommend their patients perform 150 minutes of moderate physical exercise per week[22, 23].

There were no significant differences in characteristics between the two groups[2]. 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[2]. 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).

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; $p=0.029$)[2].

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[2]. The twelve month SF-36 outcome data collected after the home-based maintenance exercise program was not incorporated in the main analysis because it was not supervised. Exercise intervention adherence and sustainability is a recognized problem in exercise interventions for older community dwelling adults[24]. At-risk and frail older adult populations tend not to maintain behavioural change or functional improvement at 12 months post intervention[25], 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[26, 27, 25, 28]. 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[29], and the ISPOR Good Research Practice Guidelines for Cost-effectiveness Analysis Alongside Clinical Trials[30].

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[31]. 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[32]. UK weights based on Brazier et al. were used[33]. 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.

2.3.2 Secondary outcome: Cardiorespiratory fitness and functional mobility

Cardiorespiratory fitness is important in addressing metabolic and cardiovascular disease 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, cardiovascular disease and functional mobility[34, 35].

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)[36]. 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.

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 $\approx$ US\$ 0.68) and adjusted to real prices in the 2018 reference year[37]. 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[38]. 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%)[39]. 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 Medical Benefits Schedule (MBS)[40]. 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[41]. 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[42].

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[43]. 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.

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.

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. 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 Chronic Disease Management Plan and cost of exercise equipment and maintenance is included as an opportunity cost in patient fees (Supplementary File 1).

Results

3.1 Costs and outcomes

Intervention costs calculated are shown in Table 1 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 1: Breakdown of costs of exercise intervention over 6 months of RCT

Intervention cost component	Cost description	Unit of measure	Cost per participant AUS
GP consent	MBS Item 23: Level B GP consultation lasting less than 20 minutes	1 consultation (\$37.05)	\$37
Registration of RCT intervention 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	On average, 4 participants 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 and fitness centres	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 medical benefits scheme; RCT randomised controlled trial; ECU Edith Cowan University; HEW higher education worker; AEP accredited exercise physiologist.

3.1.1 Outcomes

The results for the primary and secondary outcomes are reported in Table 2.

Table 2: 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 (Dominated ¹ - \$715,454)
Mean seconds change in walking time (400m walk test)	2.9	-18.6	19 ² (3.95 - 42.0)	\$29 (\$13 - \$110)

¹Fewer QALYs gained at an additional cost; ²adjusted 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 1). A cost-effectiveness plane shows the probability distribution of costs and outcomes generated by bootstrap sampling (Figure 2). 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).

--- Fig 1 Cost-effectiveness acceptability curve: QALYs - insert here---

--- Fig 2 Cost-effectiveness plane: QALYs – insert here ---

3.2 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.

3.2.1 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.

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[35]. 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[20, 21, 14-19], of which, only one was cost effective[44] and one had a high probability of cost-effectiveness[16]. 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[45-47]. 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 cardiovascular disease 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[48, 49]. As this study and others have shown, quality of life measures are not always sensitive to change, despite the beneficial outcomes of the trials[50-53]. 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[54, 47]. Recipients of curative treatment for PCa are typically younger than those with more advanced disease and the RADAR cohort were well-functioning[2], 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 multi-attribute utility instruments have recently been developed from which utilities can be derived that are more sensitive to the experience of cancer populations[55]. In addition, broader measures of quality of life such as the e-QALY, that capture benefits other than health, are also being developed[56]. These alternatives to currently existing multi-

attribute utility instruments 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 cardiovascular disease (CVD)[35] and the cardiovascular toxicity associated with ADT[57-64]. Numerous studies in the literature report on the health benefits of exercise[65, 10, 7, 5, 9, 66], particularly in relation to muscle strength and falls prevention and metabolic diseases like diabetes or CVD[67-75]. 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[29, 36]. 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.

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 6 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 6 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.

Author contributions

Kim Edmunds designed and conducted the economic analysis. Penny Reeves contributed to the design of the economic analysis and supervised the initial work. Haitham Tuffaha and Paul Scuffham made significant contributions to the final economic analysis. Mark Jones conducted the multiple imputation analysis for the economic evaluation. The exercise RCT was conducted by Daniel Galvão, Dennis Taaffe and Rob Newton in collaboration with clinicians Nigel Spry, David Joseph and Suzanne Chambers, who provided guidance in relation to the exercise intervention and RADAR clinical trial. The first draft of the manuscript was written by Kim Edmunds and all other authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest:

Scuffham is a chief investigator on the Centre for Research Excellence in Prostate Survivorship (CRE-PCS) funded by the National Health and Medical Research Council (NHMRC) (APP1120670).

Scuffham is also the recipient of a NHMRC Senior Research Fellowship (APP1136923).

Authors Edmunds, Reeves, Galvão, Newton, Jones, Spry, Taaffe, Joseph, Chambers and Tuffaha declare they have no conflicts of interest.

Ethical Approval

All procedures performed in studies involving human participants (exercise RCT) were in accordance with the ethical standards of the institutional research ethics committee (Edith Cowan University Human Research Ethics Committee HREC No. 3636) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All RCT participants provided informed consent.

Research Data Statement

Control of all primary data rests with the authors of the original exercise RCT and can be accessed by contacting Daniel Galvão (d.galvao@ecu.ed.au).

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