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

Running title:
Economic evaluation: exercise for prostate cancer

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Author contributions
Kim Edmunds, Daniel Galvão, Rob Newton, and Penny Reeves contributed to the original economic analysis conception and design. Kim Edmunds conducted the initial cost-effectiveness analysis, supervised by Penny Reeves. Haitham Tuffaha and Paul Scuffham provided intellectual guidance for the cost-effectiveness analysis. Haitham Tuffaha supervised the value of information analysis. The exercise RCT was conducted by Daniel Galvão, Rob Newton and Dennis Taaffe, Nigel Spry and David Joseph, who provided clinical guidance for the cost-effectiveness analysis. The first draft of the manuscript was written by Kim Edmunds and all authors commented on subsequent versions of the manuscript. All authors read, commented on and approved the final manuscript.

Data Availability Statement
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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

Ethical Approval
All procedures performed in the original study involving human participants were in accordance with the ethical standards of the institutional research ethics committee (Edith Cowan University Human Research Ethics Committee HREC No. 6370).

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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(Hart, Galvão, & Newton, 2017). 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(Hayes, Newton, Spence, & Galvão, 2019). 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(Hart et al., 2017). 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)(Galvão et al., 2018). 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.

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(Cormie et al., 2013). 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(Cormie et al., 2013).

The CEA was conducted from a healthcare payer perspective. The primary outcome measure was quality adjusted life years (QALYs), estimated by the area-under-the curve method 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(School of Health and Related Research (ScHaRR), 2017).

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 willingness-to-pay (WTP) at $AU50,000 per QALY, a commonly used threshold for cost-effectiveness in Australia (Henry, Hill, & Harris, 2005).

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(Organization for Economic Co-operation and Development (OECD), 2018) (AU$1 ≈ £0.56; US$ 0.68). Discounting future costs and benefits was not used due to the 12-month trial duration.

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(Tuffaha, Gordon, & Scuffham, 2014). 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(Tuffaha et al., 2014). To calculate population EVPI, the 2017 PCa prevalence was converted to absolute incidence and projected to 2028 (Australian Institute of Health and Welfare, 2019; Yu, Luo, Smith, Clements, & O'Connell, 2015). Men with metastatic cancer in Australia represent approximately 3% of this population (n=13,122)(Yu et al., 2015).

Results

Cost-effectiveness results for the three months of the pilot study are shown in Table 1. 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 1a); the probability distribution of costs and outcomes, generated by bootstrap sampling, are depicted on the cost-effectiveness plane (Figure 1b).

Table 1: 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 (Dominated[1]- $20,494)

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

Fig 1 Cost-effectiveness results: QALYs

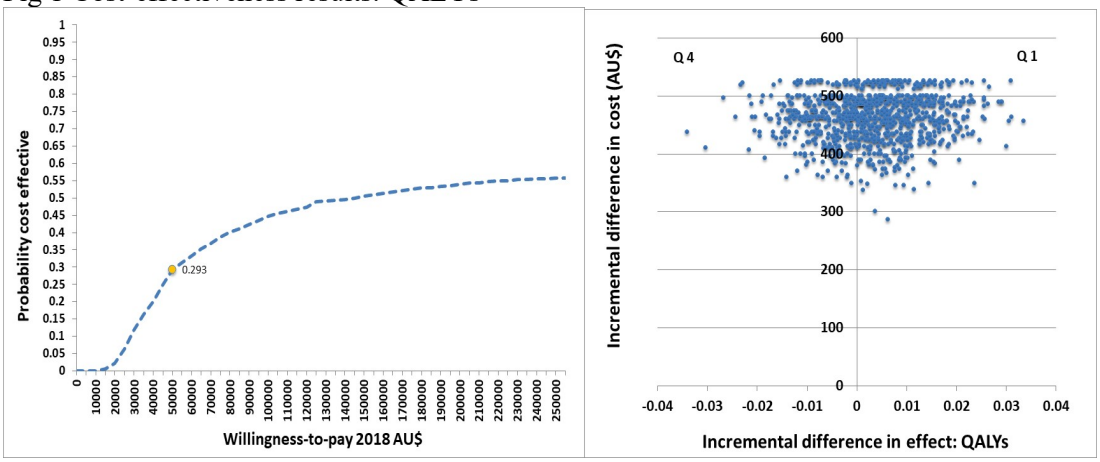

Fig 1a Cost-effectiveness acceptability curve showing probability supervised exercise intervention was cost-effective compared to usual care. Willingness-to-pay threshold AU$50,000
Fig 1b Bootstrap results on the cost-effectiveness plane: incremental costs and incremental QALYs
Q1: quadrant 1 more effective 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. If the population EVPI exceeds the expected costs of additional research, then additional research is required and worthwhile conducting (i.e., it is cost-effective to conduct further research).

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 intervention was not cost-effective at a WTP threshold of $AU50,000.

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(Cormie et al., 2013). 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. The study was conducted in the Australian setting and the results may therefore not be generalisable to other jurisdictions with different populations.

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.

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