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Evaluation of a Home-Based Walking Exercise Program on Fatigue and
Health Related Quality of Life in Prostate Cancer Patients Undergoing
Radiation Therapy: A Pilot Study.

Ciarán Patrick Doyle

Thesis submitted in accordance with the requirements for the degree of

Doctor of Public Health

University of London

May 2015

Department of Disease Control

Faculty of Infectious and Tropical Disease

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

Funded By: No funding received.

Research group affiliation: The St Luke's Radiation Oncology Network, Dublin, Ireland.

Dedications

For Catherine and Jack

Acknowledgements

Immeasurable appreciation and deepest gratitude for the help and support are extended to the following persons who in one way or another have contributed in making this study possible.

Dr Val Curtis, my research supervisor and my academic advisors: **Dr Wolf-Peter Schmidt**, **Dr Alison Tree MD**, **Dr Pierre Thirion MD** and **Ms Mary Dunne**, for their support, advice, guidance, valuable comments, and suggestions, that ensured the completion and success of this study.

I am also grateful to **The Facility of Infectious and Tropical Diseases** and the **DrPH course organisers and lecturers** for their invaluable guidance and encouragement extended to me over the years.

My sincerest thanks to the staff and patients of the **St Luke's Radiation Oncology Network**, especially the staff of **The Clinical Trials Unit** without which this research would not have been possible.

Integrating Statement

I embarked on this professional doctorate program in public health to receive training in the skills crucial for leadership roles in public health. I was attracted to the DrPH programme at LSHTM as opposed to a PhD as it is designed for students like me whose career plans involve a broader range of public health activities and not specially research. For example, as a DrPH graduate I might work in international health organisations, national ministries of health, private sector providers, not-for-profit organisations, aid agencies, consulting groups, major companies, foundations and other donors, as well as research institutions¹.

From my first day in September 2010, I found the intellectual and academic standards of the DrPH high and demanding. The awarding of the DrPH degree requires successful completion of three components: one taught element and two research outputs;

The **taught component** was delivered in Term 1 of my first year of the DrPH. This consisted of two compulsory modules which covered research methods and paradigms, the management of effective communications in public health practice and policy and leadership skills in public health. These modules are specific and exclusive to the DrPH programme and are delivered and assessed at doctoral level¹. For example I completed a systematic review of the effectiveness of plain cigarette box packaging on reducing tobacco consumption. I was then required to write a policy brief for the Minister of Health outlining my scientific findings in a language that could be easily understood by a non-scientist for making a policy decision. This assignment highlighted the importance of evidence based policy making as well as providing me with the skill set to be able to bridge the gap between the “two communities” i.e. researchers and policy makers. From a personal perspective “Leadership Management and Personal Development” gave me the opportunity to discover my personality type and consequently how to work best in teams and in leadership positions. I was required to successfully pass this taught component before moving on to the Organisational and Policy Analysis (OPA) project.

The **OPA research project** provided me with the opportunity to observe and analyse the workings of a private sector Fast Moving Consumer Goods (FMCG) company in its attempt to execute a public health objective “To increase the rates of hand washing with soap for children under five”. This OPA project involved 5 months fieldwork within my host organisation in India and Bangladesh. To achieve their public health objective it was essential that the FMCG Company form several partnerships with other private sector organisations as well as NGO’s and community based groups. I specifically analysed their current partnerships and provided recommendations on what was working and how they could improve partnerships that were proving difficult. The project was assessed on the basis of a 12,000 word academic written report. Upon successful completion of this report, I was then required to present my

organisational and policy analysis findings to the host organisation to help them make future policy decisions with regard to achieving their public health objective. This component of the DrPH provided me a unique opportunity to explore public private partnerships from both perspectives. To remain impartial in my interviewing of both sides and subsequent report for the private sector organisation developed in me a new set of communication and writing skills that I feel are essential for any future role in public health leadership.

Successful completion of the two compulsory core modules and the OPA project report was necessary to commence the current research thesis phase of the DrPH programme.

The third and final component of the DrPH programme is the **DrPH thesis**. The scope of the thesis topic is broad. It could have been from any LSHTM academic discipline and subject area, from life sciences to social sciences and not restricted to public health medicine alone or necessarily related in any way to the core taught component subjects or the topic of the OPA report.

The duration of my research and the length of the thesis itself are both shorter for the DrPH than the PhD, but the process is the same¹. For the thesis component of the degree, I was required to conduct a literature review, prepare a research protocol and receive approval of my plan from my DrPH review Committee (the equivalent of an Upgrading Committee). Following the Committee's approval and subsequent University and local ethics approval I conducted my data collection at the St Luke's Radiation Oncology Network in Ireland, analysed the results and prepared this thesis. I did this under the supervision of my Supervisor and Advisory Committee. This thesis allowed me to combine my undergraduate degree and practical experience in Radiation Oncology with my Postgraduate Masters and DrPH experience in Public health.

Declaration

I Ciarán Patrick Doyle, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Ciarán Patrick Doyle

Abstract

Background: Exercise could have a role in ameliorating some of the adverse effects of External Beam Radiotherapy and Androgen Deprivation Therapy (EBRT+ADT) in men with prostate cancer. The primary aim of this study was to assess the feasibility (process, resource and management) and efficacy (scientific) of a home-based moderate-to-vigorous physical activity (MVPA) walking exercise intervention for patients with localised prostate cancer (PCa) undergoing EBRT+ADT in anticipation of a future confirmatory RCT.

Methods: PCa patients receiving EBRT+ADT were randomized to a home-based MVPA walking intervention (n=12) or standard care (n=12) for the duration of their EBRT. Intervention patients were prescribed 3000 steps in 30 minutes on 5 days each week, i.e. a cadence of 100 steps/minute. These 3000 steps/day were prescribed in addition to their pre-determined habitual step/day. Fatigue, health related quality of life (HRQoL), anthropometric measures and physical performance were assessed at baseline (planning CT), mid EBRT, end of EBRT, and at 1 month post EBRT. Intervention participants' satisfaction with the intervention and barriers/facilitators to exercise during EBRT were also assessed. Control group participants' exercise knowledge, attitudes and practices were assessed post EBRT. The feasibility of the intervention's processes, resources and management were assessed using quantitative and qualitative methods.

Results: The exercise intervention group showed greater improvements in fatigue, quality of life, anthropometric measures and physical performance compared to standard care controls. These improvements were sustained beyond the intervention period. Exercise convenience and treatment centre environment emerged as exercise facilitators. Intervention participants' average exercise convenience and satisfaction ratings were 4.8/5 (SD=0.4) i.e. "extremely convenient" and 4.8/5 (SD=0.4) i.e. "extremely satisfied" respectively. A lack of time and poor weather emerged as exercise barriers. Standard care controls had poor exercise knowledge, attitudes and practices (KAP) post EBRT, for example only 42% of the control group were aware of the correct recommended weekly MVPA guidelines.

Conclusions: This preliminary evidence suggests that a pragmatic home-based MVPA walking exercise intervention is feasible and has the potential to evoke improvements in fatigue, in addition to other important health outcomes in men with PCa undergoing EBRT+ADT. This pilot study has achieved its six feasibility criteria and should proceed to a future confirmatory RCT.

Impact: This study shows for the first time that a pragmatic home-based MVPA walking exercise intervention using evidence based tailored exercise prescriptions is feasible and could have a positive impact on fatigue and other key outcomes in men with PCa receiving EBRT+ADT.

Definition of a Pilot Study

Investigations designed to test the feasibility of methods and procedures for later use or to search for possible effects and associations that may be worth following up in the subsequent future confirmatory study².

List of Abbreviations

Abbreviation	Full Form
ADT	Androgen Deprivation Therapy
AW	Adherence Weeks
BFI	Brief Fatigue Inventory
CAB	Complete Androgen Blockade
CONSORT	Consolidated Standards of Reporting Trials
CRF	Cancer Related Fatigue
CT	Computed Tomography Scan
DHT	Dihydrotestosterone
EA	Exercise Adherents
EBRT	External Beam Radiation Therapy
EBRT+ADT	External Beam Radiation and Androgen Deprivation Therapy
ExPx	Exercise Prescription
FACT	Functional Assessment of Cancer Therapy
FITT	Frequency, Intensity, Time and Type
HRQoL	Health Related Quality of Life
IAR	Individual Adherence Rate
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
ICORG	All Ireland Cooperative Oncology Research Group
KAP	Knowledge, Attitude, Practices
LHRH	Luteinizing-Hormone-Releasing Hormone
MVPA	Moderate to Vigorous Physical Activity
PSA	Prostate Specific Antigen
RCT	Randomised Controlled Trial
SLRON	St Luke's Radiation Oncology Network

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1. INTRODUCTION

1.1. Why Conduct A Pilot Exercise Study?

In Ireland, prostate cancer (PCa) incidence is increasing³. The number of men living as prostate cancer survivors is also increasing thanks to improved treatment and management. This simultaneous increase in incidence and survivorship has focused researchers' and clinicians' efforts on improving the health related quality of life (HRQoL) of both prostate cancer patients under active treatment, and prostate cancer survivors. A diagnosis of prostate cancer and subsequent treatment with external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) regularly causes patients to experience disease- and treatment-related adverse outcomes, such as cancer related fatigue (CRF) and decreased HRQoL and physical performance. There is strong evidence to suggest that physical activity interventions offset many of the side effects of EBRT+ADT, with few side effects themselves^{4,5}.

Large Randomised Control Trials (RCTs) are expensive and oncology trial sponsors such as the All Ireland Co-operative Oncology Research Group (ICORG) require preliminary evidence before supporting research. A pilot study is the best way to provide such evidence. Pilot studies assess the feasibility of expensive full-scale studies, and are considered an essential pre-requisite by the British Medical Council².

The current prostate cancer research at the St Luke's Radiation Oncology Network (SLRON) in Dublin, Ireland, is a pilot study. Pilot comparative randomised trials that are designed to provide preliminary evidence on the clinical efficacy of an intervention are routinely performed in many clinical areas². External pilot studies such as this study, are defined as stand-alone pieces of work, planned and carried out independently of the main future study⁶.

Methodologically rigorous pilot studies play a crucial role in health research. This study builds on the emergent exercise study methodologies in cancer populations and introduces new methods to encourage and assess exercise adherence. For example, it is the first home-based exercise intervention for PCa patients undergoing EBRT+ADT that A) utilises a tailored step-based exercise prescription and B) objectively measures physical activity adherence using a pedometer.

In addition to exploring the effect of the walking exercise intervention on participants, this pilot study enabled us to examine elements of the trials process, resources and management including: recruitment criteria and procedures, consent rate, testing of equipment, administration and assessment of the exercise intervention, and coordinating a multicentre trial.

It also served to increase our clinical experience with the new intervention for a potential future trial². Above all it aimed to determine the acceptability of the intervention to patients. To comply with best practice for reporting pilot studies, the results of this pilot investigation are reported using the CONSORT format². CONSORT guidelines also call for precise reporting of behaviour change interventions and therefore this intervention will be described according to the Behaviour Change Technique Taxonomy (v1)⁷.

To fully understand the study's outcomes of interest, objectives and methods; it is first important to have an understanding of prostate cancer, its treatment and the adverse effects of treatment.

1.2. The Prostate

The prostate (Figure 1) is a walnut sized gland found only in men. It is located between the bladder and the penis and just in front of the rectum. The urethra runs through the prostate, from the bladder to the penis, letting urine flow out of the body.

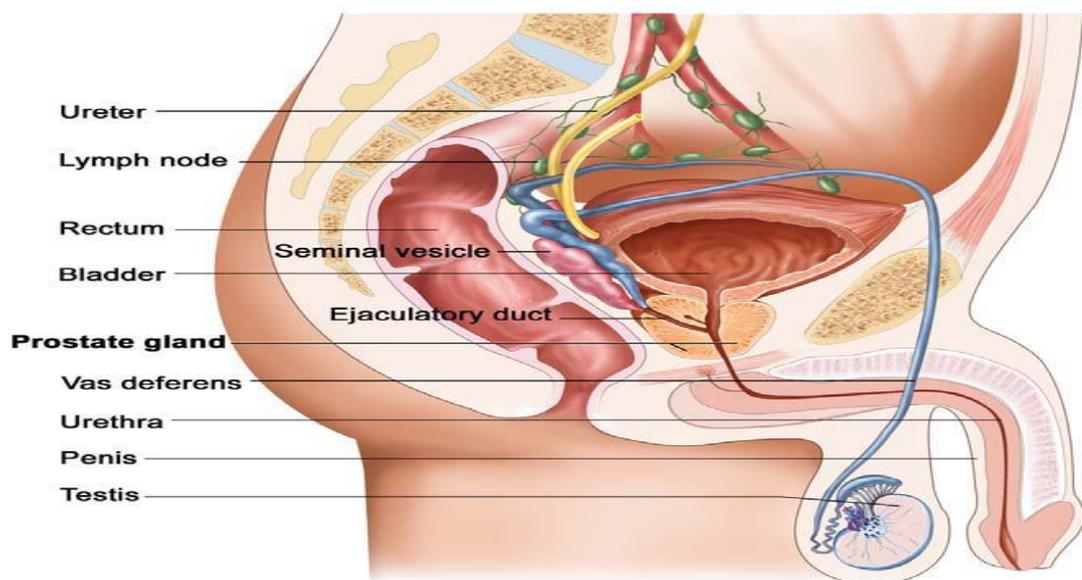


Figure 1: The Prostate

The prostate is part of the exocrine system and starts to develop before birth. It grows rapidly during puberty, fuelled by male hormones called androgens. The main androgen, testosterone, is made mainly in the testicles and to a much lesser extent in the adrenal glands. Testosterone controls the normal growth and development of the reproductive organs and is responsible for erectile function and libido. The enzyme 5-alpha reductase converts testosterone into dihydrotestosterone (DHT). DHT is the main hormone that signals the prostate to grow⁸. A normal prostate weighs between 20 and 30 grams, while a diseased prostate can weigh more than 100 grams⁸.

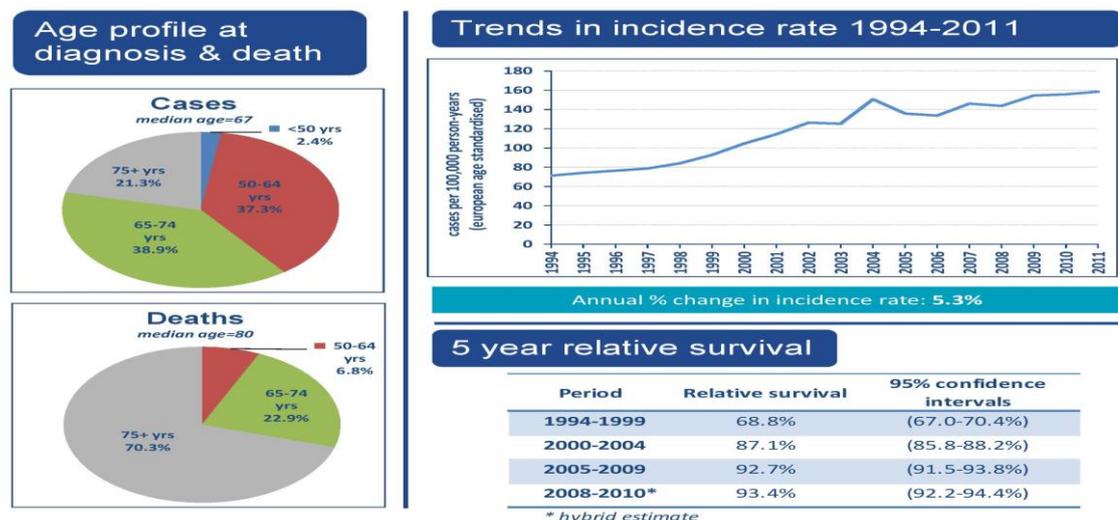
The vasa deferentia (singular: vas deferens) bring sperm from the testes to the ejaculatory ducts. The prostate secretes a milky substance that makes up around 20 to 30 percent of semen. It contains various enzymes, zinc and citric acid. Though prostate fluid is slightly acidic, another fluid in semen made by the seminal vesicles leaves semen slightly alkaline, or basic. This alkalinity helps protect sperm and prolong their life after they are deposited in the acidic environment of the vagina⁹.

The prostate can be affected by a number of disorders, including prostatitis, benign prostate hyperplasia, and cancer. If prostate cancer (PCa) develops, testosterone stimulates the PCa cells to grow. Similarly if testosterone is inhibited from acting on PCa cells, PCa cells will shrink⁸.

1.3. Prostate Cancer (PCa)

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (~13% of all deaths) in 2008¹⁰. The most recent global cancer estimates (2008) report that prostate cancer is the second most frequently diagnosed cancer of men (899 000 new cases, 13.6% of the total) and the fifth most common cancer overall¹⁰. Nearly three-quarters of the registered cases occur in developed countries (644 000 cases). Incidence rates of prostate cancer vary by more than 25-fold worldwide, the highest reported rates are in Australia/New Zealand, Western /Northern Europe, and North America, largely because the practice of prostate specific antigen (PSA) testing has become widespread in those regions¹⁰.

Prostate cancer had an estimated incidence of 3267 cases and mortality of 563 cases in Ireland in 2011³. Prostate cancer is the most common malignant cancer diagnosed in Irish men accounting for 31.9% of all invasive cancers and is the 3rd most common cause of invasive



cancer death. It has an incidence rate of 156.4 per 100,000 and mortality rate of 25.5 per

Figure 2: NCRI Prostate Cancer Fact Sheet³

100,000, cumulative lifetime risk of diagnosis of 13.5% and death of 1.1%. The National Cancer Registry predicts a 275% increase in cases between 2000 and 2020¹¹. Figure 2 below shows the age profile, trends in incidence (1994-2011), and 5 year relative survival for prostate cancer patients in Ireland.

We do not know exactly what causes prostate cancer (PCa). Researchers have found some risk factors, e.g. age, family history, race and geographic location and are trying to learn how these factors cause prostate cells to become cancerous. Essentially, PCa is caused by changes in the DNA of a prostate cell. Changes in DNA can cause normal prostate cells to grow abnormally and form cancers. DNA changes can either be inherited from a parent or can be acquired during a person's lifetime⁸.

Some genes (linear sequences of nucleotides along a segment of DNA) control when cells grow, divide into new cells, and undergo apoptosis (programmed cell death). Certain genes that tell cells to grow and divide are called oncogenes. Others that normally slow down cell division or cause cells to die at the right time are called tumour suppressor genes. Cancer can be caused in part by DNA changes (mutations) that turn on oncogenes or turn off tumour suppressor genes⁸

Ninety-five percent of PCa are of epithelial tissue with glandular origins (adenocarcinomas); other histologies (sarcoma, lymphoma, small cell carcinoma, and transitional carcinoma) are very rare. Adenocarcinomas arise in the peripheral zone of the prostate in approximately 70% of cases (figure 3).

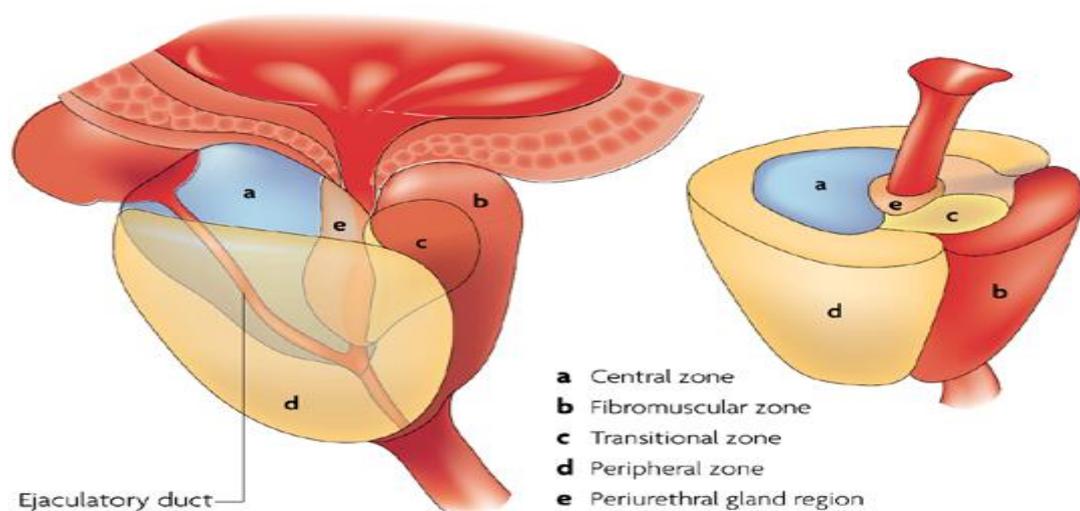


Figure 3: Zonal Predisposition to Prostate Disease

1.4. Non-Metastatic Prostate Cancer Treatment (T₁₋₃, N₀, M₀)

Cancer that is found within the gland only is called localised or early PCa. Cancer that has spread beyond the confines of prostate tissue is known as locally advanced PCa. These cancers have not spread to lymph nodes (N₀) or to distant tissues (non-metastatic or M₀) such as bones. In the T stages, the cancer is localised in the prostate gland and surrounding areas i.e. non metastatic. Among the treatment option available for non-metastatic PCa are surgery, brachytherapy (short range radiation) and the focus of this research; External Beam Radiotherapy (EBRT) and Androgen Deprivation Therapy (ADT).

Treating PCa with EBRT and ADT conveys a survival benefit for this group of patients. However, a diagnosis of non-metastatic prostate cancer and subsequent EBRT+ADT regularly causes patients to experience disease- or treatment-related adverse outcomes, which reduce patients' HRQoL during treatment and in survivorship.

1.4.1. External Beam Radiation Therapy (EBRT)

Ionising radiation causes wide-ranging molecular damage throughout cells by the production of ionised atoms, which cause breakage of chemical bonds, production of free radicals and damage to DNA. Most clinically significant effects of EBRT are due to irreparable DNA lesions which result in cell sterilisation - a loss of proliferative cells ability for sustained cell division¹².

In tumours, sterilisation of proliferative cells is a necessary condition for tumour cure. Partial sterilisation of the tumour cell population results in tumour stasis or regression, giving a clinical remission, followed by re-growth of the tumour from those cells which have retained their proliferative ability¹².

In self-renewing normal tissues, sterilisation of proliferative cells leaves the tissue unable to provide replacements for cells that are ordinarily being lost at a constant rate from the tissue, and initiates a rundown of the mature cells of the tissue. Proliferative sterilisation is often referred to as cell kill, with those cells that retain long-term proliferative ability being described as survivors¹².

In radical EBRT the objective is complete sterilisation of any tumour cells present without incurring a high risk of serious injury to normal self-renewing tissues for e.g. bladder and rectal tissue. EBRT side effects or "toxicities" can be divided into two categories; Acute- occurring during or shortly after EBRT, and Late- toxicities which manifest months or even years after the completion of EBRT.

The most commonly reported radiation induced acute toxicity of EBRT is Cancer Related Fatigue (CRF). EBRT has been reported to induce acute fatigue in up to 80% of patients¹³. In general, CRF usually increases in severity during EBRT, and peaks at the completion of EBRT. In up to 30% of cases, radiation-induced fatigue can last long after completion of treatment and thus develop into chronic fatigue^{13,14}. Other commonly reported acute effects are listed in table 1. Rectal bleeding and urinary function toxicities are the most commonly reported late toxicities of EBRT; however serious toxicities are very rare.

Irritation and inflammation of the bladder	Increased urgency/frequency of urination Nocturia (increased night-time urination) Dysuria (painful urination)/Haematuria (blood in urine) Incontinence Urinary tract obstruction or pain,
Irritation and inflammation of the rectum	Diarrhoea/Constipation Proctitis (inflammation of the rectum) Rectal pain/bleeding/mucous discharge

Table 1: Potential Acute Side Effects of EBRT

1.4.2. Androgen Deprivation Therapy (ADT)

Around 50% of men will be undergo Androgen Deprivation Therapy (ADT) as part of their treatment¹⁵. The purpose of ADT is to reduce levels of the androgens - testosterone and dihydrotestosterone (DHT) in the body, or to prevent them from reaching prostate cancer cells. Most of the male body's androgens come from the testicles, but the adrenal glands also make a small amount. Androgens stimulate prostate cancer cells to grow. Lowering androgen levels or stopping them from getting into prostate cancer cells often makes prostate cancers shrink or grow more slowly for a time. However, hormone therapy alone does not cure prostate cancer and eventually, it stops controlling the disease¹⁶.

There are several clinical situations when ADT may be prescribed¹⁶ for example: if patients' are not able to have surgery/EBRT or can't be cured by these treatments because the cancer has already spread beyond the prostate gland, if a patient's cancer remains or comes back after treatment with surgery or radiation therapy, or before EBRT to try to shrink the cancer to make treatment more effective.

In the current research, we are only concerned with men who receive ADT along with EBRT (EBRT+ADT) as their initial treatment. These patients receive EBRT+ADT because they are at higher risk of the cancer coming back after treatment. This risk is determined by combining three pieces of clinical information about the cancer:

A) Gleason score (pathology), a score given to a prostate cancer based upon its microscopic appearance. Cancers with a higher Gleason score are more aggressive and have a worse prognosis.

B) PSA level (blood), and

C) T-stage (growth of the cancer inside/outside the prostate as assessed clinically by a Digital Rectal Exam (DRE) or radiologically by an MRI scan).

Patients with one high risk factor e.g. Gleason score ≥ 8 or PSA ≥ 20 or T-stage of “3” are usually prescribed a short course of ADT i.e. 6 months. Patients with two or more high risk factors are normally prescribed long-term ADT i.e. 2-3 years. Patients receiving EBRT+ADT are at a greater risk of some treatment induced toxicities due to the combined effects EBRT+ADT than if receiving either alone. Patient on long-term ADT are more likely to experience adverse effects than those on short-term courses.

Several types of hormone therapy can be used to treat prostate cancer. Some lower the levels of testosterone or other androgens. Others block the action of those hormones¹⁶. Most patients are prescribed a combination of a) luteinizing hormone-releasing hormone (LHRH) analogs and antagonists and b) anti-androgens.

a) Luteinizing hormone-releasing hormone (LHRH) analogs and antagonists

LHRH analogs e.g. Decapeptyl[®] and Eligard[®], and antagonists e.g. Firmagon[®] lower the amount of testosterone made by the testicles. LHRH analogs are injected or placed as small implants under the skin. Depending on the drug used, they are prescribed from once a month up to once every 6 months. When LHRH analogs are first given, testosterone levels go up briefly before falling to very low levels. This effect is called ‘flare’ and results from the complex way in which LHRH analogs work. Flare can be avoided by giving drugs called anti-androgens (see anti-androgens below) for a few weeks when starting treatment with LHRH analogs. LHRH antagonists work like LHRH agonists, but they reduce testosterone levels more quickly and do not cause tumour flare like the LHRH agonists do. Degarelix is an example of an LHRH antagonist.

b) Anti-androgens

Androgens have to bind to a protein in the cell called an androgen receptor in order to work. Anti-androgens e.g. Casodex[®] stop androgens from working by binding to the receptors so the androgens can't. Drugs of this type, such as flutamide, bicalutamide, and nilutamide, are taken daily as pills. Anti-androgens are not often used by themselves. An anti-androgen may be added to treatment if an LHRH analog or antagonist is no longer working by itself. An anti-androgen is sometimes given for a few weeks when an LHRH analog is first started to prevent a tumour

flare. Anti-androgen treatment may be combined with LHRH analogs as first-line hormone therapy. This is called combined androgen blockade (CAB).

While ADT has the beneficial effect of slowing down the growth of cancer by reducing the production of testosterone, this reduction leads to adverse effects (table 2) involving changes in body composition and fatigue that may reduce patients' Health related Quality of Life (HRQoL). ADT has some adverse effects in common with EBRT, namely CRF and decreased physical performance. It is suggested that 40% of men with biochemically controlled prostate cancer on long-term ADT report CRF that interferes with functioning¹⁷.

Skeletal	Decreased bone mass density Increased osteoporosis incidence Increased fracture risk
Body Composition	Increased body fat Decreased lean body mass
Functional	Decreased muscle strength Decreased physical performance
Cardiovascular /Metabolic	Increased circulating triglycerides Increased high density lipoprotein and total cholesterol Increased insulin resistance Increased incidence of metabolic syndrome and diabetes Increased arterial stiffness
Sexual	Erectile dysfunction Loss of Libido Gynecomastia
Other	Increased fatigue Decreased QoL Increased depression Decreased Cognitive function Vasomotor flushing (Hot Flushes)

Table 2: Adverse effects of ADT¹⁸

Since the incidence of PCa is increasing and the number of men living as prostate cancer survivors is increasing, research and clinicians' efforts on improving CRF and overall health related quality of life (HRQoL) of both prostate cancer patients under active treatment, and prostate cancer survivors is also increasing. Key to this effort is reducing the onset and effects of EBRT+ADT treatment related toxicities and consequently reducing the future burden on the public health system.

1.5. Public Health Burden

Whilst EBRT+ADT convey clear biochemical failure-free survival and overall survival benefits for non-metastatic PCa patients CRF and combined EBRT+ADT treatment related changes in body composition may lead to diseases and syndromes that are more of a public health burden than the prostate cancer itself.¹⁵

As prostate cancer patients undergoing EBRT+ADT are likely to experience a diminished level of physical and psychological functioning that persists even after treatment finishes, intervention strategies that mitigate the effects of the associated CRF and overall HRQoL are essential^{4,5,19,20} and the driving force behind the current research.

The next chapter (Literature review) will discuss in more detail the relationship between PCa treatments, Health related Quality of Life (HRQoL), Cancer Related Fatigue (CRF) and their implications for the future health of PCa survivors. It will also outline the evidence based decision-making process that has led to the conclusion that there is a need assess the feasibility (process, resource and management) and efficacy (scientific) of a home-based moderate to vigorous physical activity (MVPA) walking exercise intervention for prostate cancer (PCa) undergoing EBRT+ADT in anticipation of a future confirmatory RCT at SLRON.

2. LITERATURE REVIEW

This review of the literature is divided into four sections. Section 2.1 explores the relationship between Prostate cancer treatment, HRQoL and CRF, followed by a review of the literature regarding interventions designed to ameliorate HRQoL and CRF.

Section 2.2 systematically reviews the literature regarding physical activity interventions for men with prostate cancer actively undergoing treatment with EBRT+ADT

Section 2.3 examines the literature regarding best practices for prescribing exercise and enhancing adherence to the exercise prescription and finally section 2.4 draws these sections together to conclude the literature review and contextualise the present study and provide justification for its research objectives.

2.1. Prostate Cancer Treatment - Health Related Quality Of Life and Fatigue

A diagnosis of prostate cancer and subsequent external beam radiotherapy (EBRT) and androgen deprivation therapy (ADT) regularly causes patients to experience disease- or treatment-related adverse outcomes or both¹⁵, which reduce health related quality of life (HRQoL).

Although there is no universally accepted definition of HRQoL, there is a consensus that it is a patient-reported, multidimensional construct⁵ with four major domains; physical function, psychological function, economic and social function, and spiritual wellbeing. HRQoL also encompasses the negative aspects of the disease or treatment such as fatigue²¹. Common psychological and emotional adverse outcomes include depression, anxiety, stress, reduced self-esteem, loss of sense of control, and reduced psychological and emotional well-being^{5,20,22,23}.

The physical and functional adverse outcomes of prostate cancer and its treatment include diminished cardiovascular and pulmonary function, decreased strength and lean body mass, weight change, interrupted sleep patterns and, most notably for patients, cancer related fatigue (CRF)^{5,20,22,23}. These physical and functional adverse outcomes are considered more clinically significant by clinicians and cancer researchers alike than social/family or emotional wellbeing adverse outcomes.

2.1.1. External Beam Radiotherapy

Cancer Related Fatigue (CRF) is the most commonly reported long-term adverse outcome in men treated for prostate cancer. CRF is defined by the National Cancer Control Network as a “*distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and*

*interferes with usual functioning*²⁴. It is considered as important as lower urinary tract symptoms (LUTS) in its influence on HRQoL during and after EBRT¹³

The exact physiological cause of CRF is unknown, but it is thought to reflect central nervous system mechanisms¹⁵. Its aetiology, correlates and prevalence in the context of cancer of the prostate are poorly understood by clinicians²⁵. To the best of the author's knowledge, no study has examined the severity and correlates of fatigue in men receiving EBRT+ADT.

Radiotherapy has been reported to induce acute fatigue (during or soon after EBRT) in up to 80% of patients¹³. In general, during EBRT, CRF usually increases in severity and peaks at the completion of RT. It can have a profound effect on patients' ability to function in their usual roles and activities²⁵. In about 30% of cases, radiation induced fatigue can last long after completion of treatment and thus develop into chronic fatigue^{13,14}.

There appears to be no consensus on how cancer patients in general experience fatigue with respect to EBRT field size, radiation dose, number and frequency of treatment fractions and EBRT free days¹³. In addition, there is conflicting evidence relating to the relationship between fatigue and demographic and social factors, in particular age, gender and marital status²⁶. However, there is evidence that suggests that treatment modality, e.g. active surveillance, ADT, RT, and surgery, affect prostate cancer patients' fatigue levels, with the highest levels of fatigue measured in the RT+ADT group²⁷.

2.1.2. Androgen Deprivation Therapy

Around 50% of prostate cancer patients will use ADT as part of their treatment¹⁵. While ADT has the beneficial effect of slowing down the growth of cancer by reducing the production of testosterone, this reduction leads to side effects that increase CRF and reduce HRQoL. Reductions in testosterone directly contribute to substantial declines in body composition. Galvao et al²⁸ reported regional decreases in bone mineral density (1.3-3.9%) and muscle mass (1.4 -5.6%), and increases in fat mass (12.0 – 20.7%), after 36 weeks on ADT. These changes in body composition and CRF may contribute to significant reductions in aspects of physical fitness and functional performance. Prostate cancer patients on ADT have the physical fitness and functional performance ability of someone 10-20 years older^{15,29}.

These declines contribute to prostate cancer patients having up to four times more fall-related skeletal fractures (non-pathological) than aged matched controls^{15,30}. Further, changes in body composition and reduced physical activity levels often lead to serious changes in blood pressure, blood lipid profile and other contributory factors for metabolic syndromes- a name for a group of risk factors that occur together and increase the risk for coronary artery disease, stroke and type-2 diabetes. Keogh *et al*¹⁵ illustrate the relationship between changes in these measures (Figure 4)

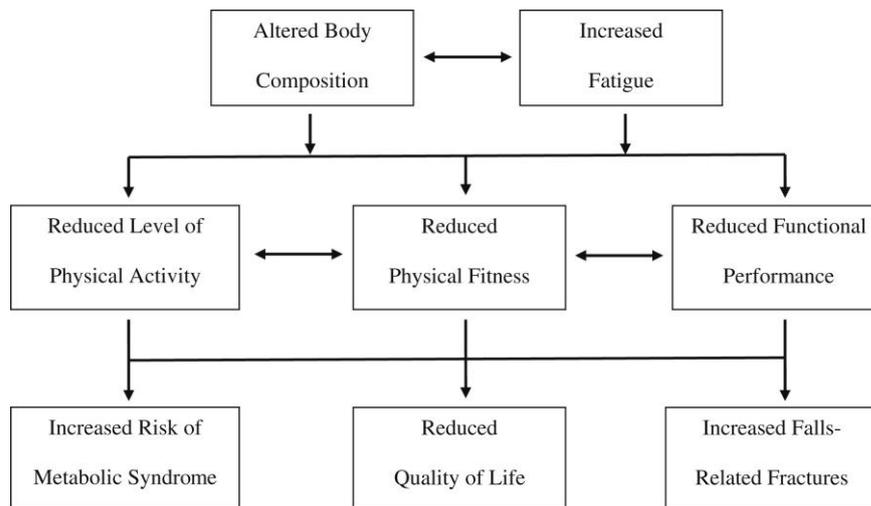


Figure 4: Potential Interrelationships between Changes in Outcome that may Contribute to an Increased Risk of Metabolic Syndrome, Falls Related Fractures and Reduced QoL for PCa Patients Undergoing EBRT+ADT¹⁵

Despite current multimodal approaches to ameliorate CRF and HRQoL including patient education, pharmaceutical agents, aetiology-specific interventions, and non-pharmacological therapies, patients in SLRON and other cancer centres continue to suffer from CRF and subsequent reductions in HRQoL.

The literature strongly supports the conviction that as PCa patients are extremely likely to experience a diminished level of HRQoL that persists even after treatment finishes, intervention strategies that mitigate the effects of the associated CRF and physical performance deterioration are essential ^{4,5,19,20}.

2.1.3. Physical Activity Interventions for Cancer Patients

A number of QOL interventions for cancer patients have been reported. Meyer and Mark, as cited by Courneya and Friedenreich²⁰, systematically reviewed the psychosocial therapies: cognitive behavioural therapies, informational and educational strategies, individual counselling or psychotherapy, social support and alternative treatments such as music therapy. They reported that these therapies are least likely to address the physical and functional problems encountered by cancer patients, which experts consider the most important dimensions of overall QOL.

There is strong evidence to suggest that physical activity interventions offset many of the side effects of EBRT+ADT with few side effects itself^{4,5}. Researchers suggest that physical deconditioning, as a consequence of diminished physical activity, resulting from either the cancer itself or its treatment, produces reductions in aerobic capacity and ultimately causes CRF¹⁴. CRF interferes with the ability to pursue occupational and social activities, consequently diminishing HRQoL.

A 2012 Cochrane review of 56 Randomised Controlled Trials (RCTs) with 4068 patients examined exercise for the management of fatigue in patients with all cancer diagnoses⁴. Another 2012 Cochrane review⁵ of 56 RCTs with 4826 participants examined exercise interventions on HRQoL for people with all cancer diagnoses during active treatment. The findings of these reviews need to be considered cautiously because they looked at many different variables and there was no consistency in the tools used to measure primary endpoints (HRQoL or fatigue)⁵. The combined 81 interventions differ across 11 dimensions including cancer diagnosis, outcome measures, mode, frequency, duration, location and format of exercise intervention.

Meta-analyses indicated that exercise interventions compared with control interventions had a positive impact on overall HRQoL and certain HRQoL domains including physical, functional and social functioning at varying follow-up periods for cancer patients. Fatigue data were independently assessed and synthesised in both systematic reviews. Exercise interventions were statistically significantly more effective for reducing fatigue than the control intervention at the end of the intervention period and at 12 weeks' follow-up. The Cochrane reviews also revealed insights such as:

- a) the benefits of exercise on fatigue were only observed for interventions during or post-adjuvant cancer treatment for prostate cancer patients,
- b) aerobic exercise significantly reduced fatigue but resistance exercise and other forms of exercise did not have a statistically significant effect,⁴
- c) there was a greater improvement in HRQoL and physical functioning, and a greater reduction in fatigue when prescribed a moderate or vigorous versus a mild exercise program⁵ as compared with light exercise programs.

In view of the above, section 2 aims to systematically review the literature regarding physical activity interventions for men with prostate cancer actively undergoing treatment with EBRT+ ADT and to contextualise the present study and provide justification for its research objectives.

This review will focus on examining the effectiveness of exercise interventions on CRF and HRQoL. To achieve this aim, study outcomes like changes in physical fitness and functional performance parameters (table 5), and exercise intervention related changes in quality of life (QoL) type measures (table 6) are examined. An examination of exercise intervention prescription and patient adherence will also be conducted.

The findings of this review inform the current pilot exercise intervention study and potential clinical trial in the St Luke's Radiation Oncology Network (SLRON).

2.2. Systematic Review

Section 2.2 aims to systematically review the literature regarding physical activity interventions for men with prostate cancer actively undergoing treatment with EBRT+ADT and to contextualise the present study and provide justification for its research objectives.

2.2.1. Literature Search Methods

In order to systematically review the literature regarding physical activity interventions for men with prostate cancer actively undergoing treatment with EBRT+ ADT, PubMed, Medline, Cochrane Library, TRIP database and Google Scholar were searched using the key words: prostate cancer, radiotherapy, fatigue, cancer-related fatigue, exercise, physical activity, QoL and their derivatives. Additional searches were conducted using the reference list and appropriate MeSH terms from two Cochrane reviews identified in the original search and by contacting authors. To be considered eligible for inclusion articles had to be full articles published in peer-reviewed journals and include prostate cancer patients only or, if a mixed study, report outcomes for prostate cancer patients separately. In addition, only articles describing exercise intervention for patients actively undergoing EBRT+ADT were included. There were no restrictions on language or year published. To the best of our knowledge this is the only review of such studies.

2.2.2. Data Analysis

The design and methodological rigor of each study was critically evaluated using a modified version of Sackett's method as described by Keogh and MacLeod¹⁵ and Megens and Harris³¹. The following criteria were adapted from Sackett's rules for scientific evidence: (1) inclusion and exclusion criteria were listed for the subjects and clearly stated whether patients were actively receiving radiotherapy (2) the mode of physical activity (aerobic and or resistance) was adequately described so as to be replicable, (3) the reliability of data obtained with outcome measures was investigated, (4) the validity of the outcome measures had been assessed, (5) the assessors were blinded to the treatment groups, and (6) all subjects enrolled in the study were accounted for in analysis. This method has been used in previous systematic reviews of intervention studies involving cancer patients and complies with the PRISMA statement on best practice for reporting systematic reviews¹⁵.

The five levels (1-5) of evidence devised by the University of Oxford's Centre for Evidence Based Medicine (March 2009)³² were utilised in conjunction with Sackett to provide four grades (A-D) of recommendations for the benefits of aerobic and or resistance exercise interventions for prostate cancer patients actively undergoing EBRT+ADT.

Grade A recommendations were given to studies with strong evidence supported by at least one Level I study e.g. An RCT involving > 100 participants. Grade B recommendation were given

to studies with relatively strong evidence supported by at least one Level II study e.g. An RCT involving < 100 participants). Grade C recommendations were given to studies with moderate/moderately weak evidence supported by a corroborative study other than a RCT (Level III – IV studies). There were no Grade D recommendations i.e. studies with troublingly inconsistent or inconclusive studies at any level

2.2.3. Results

2.2.3.1. Description of Studies

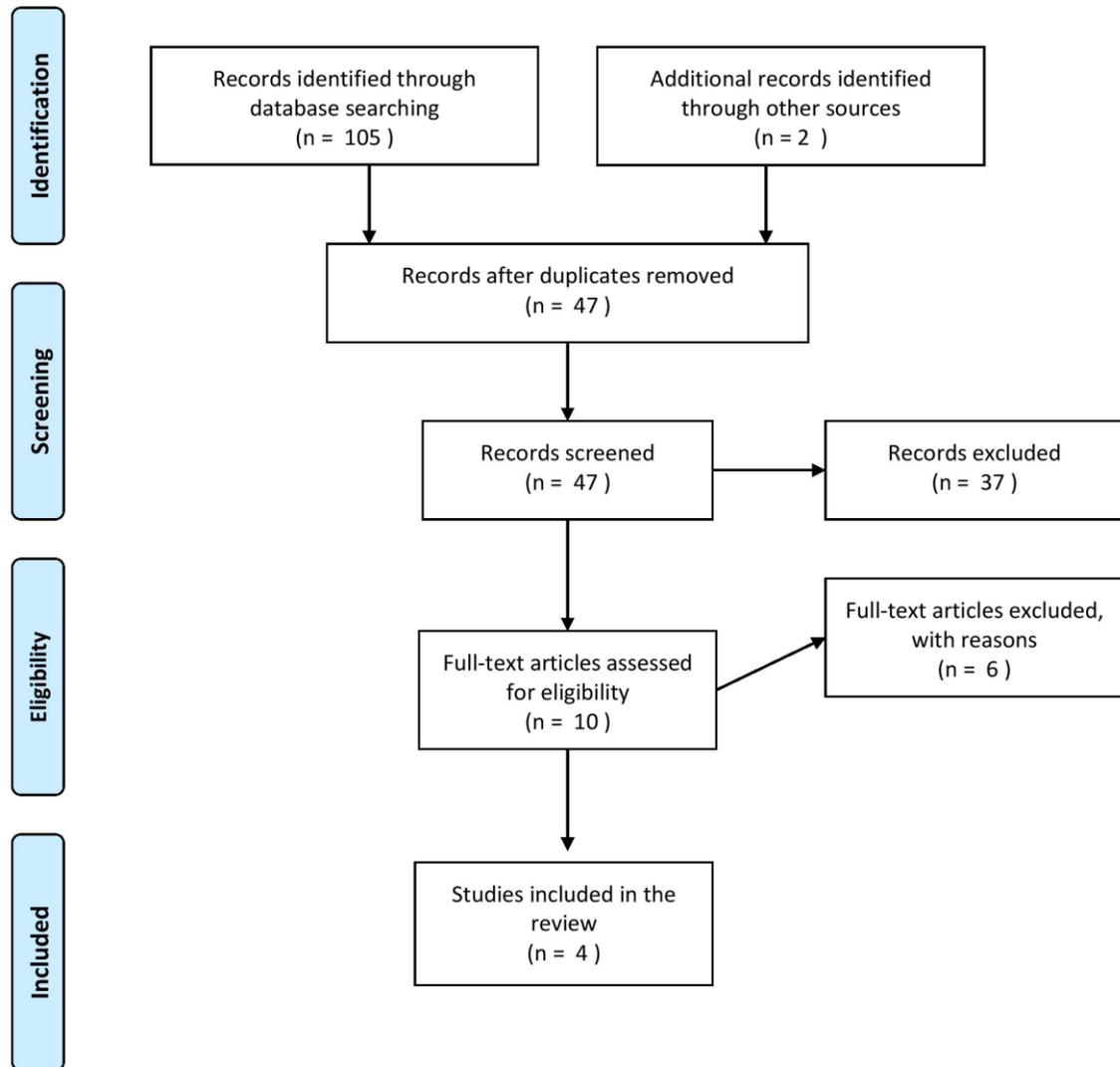


Figure 5: PRISMA Flow Diagram

Ten studies involving prostate cancer patients receiving exercise interventions were identified. Of these ten, only four met the principal inclusion criteria for this review (actively undergoing EBRT+ADT). Of the four included studies one was categorised as level Ib³³, and the remaining three as level IIb³⁴⁻³⁶. All four studies were RCTs and had clearly outlined their inclusion and exclusion criteria (e.g. absence of distant metastasis and the ability to participate in an exercise intervention). All studies gave detailed descriptions of how they structured their exercise

interventions. Three studies investigated aerobic interventions only³⁴⁻³⁶ while one study investigated both aerobic and resistance interventions³³.

Two studies identified fatigue and/or HRQoL as their primary outcome^{33,34}, the other two^{35,36} did not specify primary outcomes. All studies used reliable and valid measures of fatigue and HRQoL. Fatigue was measured using the Functional Assessment of Cancer Therapy-Fatigue^{33,36} (FACT-F), the Brief Fatigue Inventory³⁵ (BFI) or Piper Fatigue Scale³⁶ (PFS) instruments. HRQoL was measured using the Functional Assessment of Cancer Therapy-Prostate^{33,36} (FACT-P) instrument.

One study³³ measured muscular endurance by assessing trends in participants' performance of two sets of eight to twelve repetitions of ten different exercises using a weight of 60-70% of one repetition max (1RM). Aerobic endurance was measured in three studies using walking tests³⁶, volume of oxygen consumed³³ or shuttle walking tests³⁵. Functional performance was only measured in one study and they used a sit-to-stand test³⁶ which predicts physical function and falls risk¹⁵.

None of the four studies used blind assessment of outcomes; this can be largely explained by the nature of interventions. Three of the four studies accounted for attrition^{33,34,36}. A summary of this evaluation can be found in table 3.

The level of demographic information and clinical description of participants' prostate cancer and treatment varied greatly between the four studies. The average age of participants in intervention arms was 67 years. Only one study³⁶ reported race and their intervention included 27% white, 64% black and 9% Hispanic participants. Two studies reported education level with the majority of participant having achieved a college or University education³³ or over 12 years in education³⁶ Only one study reported working status and reported that 22% of the intervention arm were in full-time employment versus 34% in the control arm³³. The majority of patients presented with T1/2 and stage 2 tumours. Only one study reported the average risk category (high) and Gleason score (7) of patients' tumours and length of time on ADT (12 months)³⁴. Two studies^{33,36} reported the average weight of participants (88.6 kg) while only one reported Body Mass Index (BMI) (28.9)³³. Time since diagnosis and presenting psa level were not reported in any study.

Two of the studies consisted of group-based exercise^{33,36} and two consisted of home-based exercise^{34,35}. Aerobic exercise was the primary focus of three studies³⁴⁻³⁶ and comparing aerobic and resistance exercise was the focus of one study³³. The results of the eligible studies are summarised in tables 4-6.

Table 4 presents the results of the only study to assess a change in body composition. This group-based study compared aerobic versus resistance exercise for changes in body fat

percentage. It reported that resistance exercise caused a nonsignificant decrease in fat percentage while participants undergoing the aerobic exercise intervention actually increased the body fat percentage. From baseline to post-test (24 weeks) the % body fat change of participants was -0.4%, +1.4 % and + 1.6%³³ for those in the Resistance exercise, Aerobic exercise, and control /usual care groups respectively.

Table 5 presents the results of exercise intervention related changes in physical fitness and functional performance parameter measures for prostate cancer patients undergoing radiation therapy in the four studies.

Only one study³³, which was group-based, and compared aerobic to resistance exercise, assessed changes in muscle endurance. It reported a significant increase in the resistance exercise group and a nonsignificant increase in the aerobic exercise group. Three studies^{33,35,36} assessed aerobic endurance and reported significant increases for both home and group-based interventions and aerobic and resistance interventions. One group-based aerobic intervention observed nonsignificant results³³. One study assessed functional performance and found a significant improvement in a sit-stand-test post a group-based aerobic exercise intervention.

Table 6 presents the results of exercise intervention related changes in QoL type measures for prostate cancer patients undergoing radiation therapy. Significant increases in QoL were reported for both aerobic³⁶ and resistance³³ group-based interventions. Only a group-based aerobic intervention showed a significant decrease in fatigue³³. Home-based aerobic interventions showed increases in QoL³⁴ and significant decreases in fatigue post intervention³⁵.

Only one study, *Truong et al*³⁴ considered adherence to exercise prescription.

2.2.4. Grade Recommendations

Based on the results summarised in table 4 “Exercise Related Changes in Body Composition for Prostate Cancer Patients Undergoing EBRT”, table 5, “Exercise Intervention Related Changes in Physical Fitness and Functional Performance Measures for PCa Patients Undergoing EBRT” and table 6 “Exercise Intervention Related Changes in Quality Of Life Type Measures for PCa Patients Undergoing EBRT” recommendations on the benefits of aerobic or resistance exercise as well as group- and home-based interventions are suggested in table 7¹⁵.

Table 3: Evaluative Criteria for the Exercise Intervention Studies Reviewed

Study	Level of Evidence	Inclusion and Exclusion Criteria	Treatment can be replicated	Reliability of Outcome Measures	Validity of Outcome Measures	Blind assessment of Outcome measures	Account for Attrition (reporting bias)
Group-Based exercise							
Monga et al ³⁶	Level II b	Y	Y	Y	Y	N	Y
Segal et al ³³	Level I b	Y	Y	Y	Y	N	Y
Home-Based Exercise							
Truong et al ³⁴	Level II b	Y	Y	Y	Y	N	Y
Windsor et al ³⁵	Level II b	Y	Y	Y	Y	N	N

Y = Yes, N = No

Note: Due to the nature of exercise interventions, all studies were at high risk for *performance and detection bias*

Level

- 1a Systematic Reviews (SRs) of Randomised Controlled Trials (RCTs)
- 1b Individual RCT (with narrow Confidence Interval‡)
- 2a SRs of cohort studies
- 2b Individual cohort study (including low quality RCT; e.g., <80% follow-up)

Table 4: Exercise Related Changes in Body Composition for Prostate Cancer Patients Undergoing EBRT

Study	Participants (n) Mean Age (years)	Form of Training	Duration (Weeks) & Frequency (Per Week)	Mean change in Body fat % from baseline to Post-Test (p-value)	Adjusted* Group difference in mean change from baseline to post-test (p-value)
Group-Based Exercise					
Segal et al ³³	(41) 65	UC	24,3	+1.60 (.003) ¹	RT vs. UC: -1.50 (.055) AT vs. UC: -0.15 (.847)
	(40) 66	RT		-0.04 (.947)	
	(40) 66	AT		+1.40 (.016) ¹	

UC: Usual Care; RT: Resistance Training; AT: Aerobic Training.

* Adjusted for age, cancer stage, androgen deprivation therapy (yes/no), and Gleason score.

1. Indicates significant (p<0.05) improvement.

Table 5: Exercise Intervention Related Changes in Physical Fitness and Functional Performance Measures For PCa Patients Undergoing EBRT

Study	Participants (n) Age in Years	Form of Training	Duration (Weeks) Frequency (Per Week)	Muscular Endurance	Aerobic Endurance	Sit to Stand
Group-Based Exercise						
Monga et al ³⁶	(11) 68	AT	8;3		+47% METS treadmill ¹	15% Faster in 5 STS ¹
Segal et al ³³	(40) 66	RT	24;3	+24-25% ¹	+9% treadmill VO ₂ max ¹	
Segal et al ³³	(41) 66	AT	24;3	+3-7%	+5% treadmill VO ₂ max	
Home-based exercise						
Windsor et al ³⁵	(33) 68	AT	4; ≥3 encouraged		+ 13 % shuttle walk ¹	

RT = resistance training; 5STS = five sit to stand test; AT = aerobic training; METS = metabolic equivalents during a treadmill test. VO₂ max (is the maximum capacity of an individual's body to transport and use oxygen during incremental exercise, which reflects the physical fitness of the individual. The name is derived from V - volume, O₂ - oxygen, max - maximum.

1. Indicates significant (p<0.05) improvement.

Table 6: Exercise Intervention Related Changes in Quality Of Life Type Measures for PCa Patients Undergoing EBRT

Study	Participants (n) Age in Years	Form of Training	Duration (Weeks) Frequency (Per Week)	Overall QoL	Social Quality Of Life	Physical QoL	Fatigue
Group-Based Exercise							
Monga et al ³⁶	(11), 68	AT	8;3	+10% FACT-P ¹	+14% FACT-P ¹	+15% FACT-P ¹	-179% PFS ¹
Segal et al ³³	(40) 66	RT	24,3	+5% FACT-P ¹			-11% FACT-F
Segal et al ³³	(41) 66	AT	24,3	+3% FACT-P			-6% FACT-F
Home-based exercise							
Truong ³⁴	(50) 67	AT	12;3	Higher fatigue interference trends with QoL observed in control compared with exercise group			Stable mean total fatigue scores from baseline to 6 mts post-EBRT FU (P=0.52) Fatigue in control subjects escalated from baseline to 6 mts post-EBRT (P ≈ 0.3) (BFI)
Windsor et al ³⁵	(33) 68	AT	4; ≥3 encouraged				-82% BFI ¹ (estimated)

RT = resistance training; AT = aerobic training; FACT-P = functional assessment of cancer therapy-prostate questionnaire; FACT-fatigue = functional assessment of cancer therapy-fatigue questionnaire; PFS = piper fatigue scale; BFI = brief fatigue inventory.

1. Indicates significant (p<0.05) improvement.

Table 7: Summary of Recommendations from 4 Studies on the Benefits of Exercise Interventions for PCa Patients Undergoing EBRT

	Group-based Exercise (n=2) ^{33,36}	Home-Based Exercise (n=2) ^{34,35}	Resistance Training (n=1) ³³	Aerobic Training (n=4) ³³⁻³⁶
Body Composition				
Fat Mass	NSE	NA	NSE	NSE
Physical Fitness				
Muscular Endurance	A	NA	A	NSE
Aerobic Endurance	A	B	A	B
Functional Performance				
Sit to Stand	B	NA	NA	B
Quality of Life				
Overall	A	NSE	A	NSE
Social	B	NA	NA	B
Physical	B	NA	NA	B
Fatigue	B	B	NSE	B

Grade A recommendation = strong evidence supported by at least one Level I study e.g. An RCT involving > 100 participants

Grade B recommendation = relatively strong evidence supported by at least one Level II study e.g. An RCT involving < 100 participants)

Grade C recommendation = moderate/moderately weak evidence supported by a non-RCT that is Level III – IV studies)

Grade D recommendation = troublingly inconsistent or inconclusive studies at any level

NA = not assessed in any study in this category

NSE = study (s) in this category reported no significant effect

2.2.5. Discussion

A lack of research concerning PCa patients and the effects of EBRT+ADT is evident considering that there is only one relatively large study (100+ participants) and three smaller studies included in this review. This trend is also apparent from previous Cochrane reviews where the majority of studies focus on breast cancer patients, fatigue and QoL issues.

Applying the rules of evidence suggested by the University of Oxford's Centre for Evidence Based Medicine, provides relatively strong (Grade B) to strong (Grade A) evidence that exercise interventions performed at least three times per week can significantly increase physical fitness, functional performance and QoL, and can decrease fatigue in prostate cancer patients actively undergoing RT+ADT. The strongest evidence for improved physical fitness and QoL came from group-based (Grades A and B) resistance exercise (Grade A) interventions. A clear gap in the literature regarding scientific justification for exercise prescription and exercise adherence evaluation is apparent.

2.2.5.1. Body Composition

Changes in body composition (% body fat) was only reported in one group-based study³³ and was non-significant for both aerobic and resistance interventions, compared to usual care, although the resistance exercise group did show a trend towards a small reduction in body fat (see Table 4). This lack of improvement is most likely as a result of muscle loss combined with weight gain due to hormone therapy¹⁵. Unfortunately this study does not provide details of length of time on ADT or type of ADT. Encouragingly both resistance and aerobic exercise had a more positive effect on the percent of body fat for patients on the exercise intervention group than for those in the control group. The ability to retard a percentage body fat increase, in this group of patients, can potentially provide significant public health benefits in the future, in particular by decreasing the risk factors of metabolic syndrome.

2.2.5.2. Aerobic Vs. Resistance Exercise Interventions

Aerobic exercise interventions provide level B evidence for improvements in functional performance and the social and physical domains of QoL. Authors of resistance exercise studies did not record these outcomes so a comparison is impossible. The lack of recorded/ reported data on functional performance outcomes and the social and physical domains of QoL outcomes in resistance exercise studies was unexpected. These outcomes are useful predictors of QoL and future health.

Resistance training interventions provided Level A evidence for improvements in the physical fitness domains of muscle endurance and aerobic endurance compared with no significant effect and Level B evidence for aerobic exercise interventions.

Resistance training provided Level A evidence for improvements in overall QoL whereas aerobic exercise surprisingly had no significant effect. On the other hand aerobic exercise

provided Level B evidence for an improvement in fatigue compared to resistance exercise which appeared to have no significant effect.

2.2.5.3. Group-Based Vs. Home-Based Exercise Intervention

Group-based exercise interventions provide level A and B evidence for improvements in physical fitness, functional performance and social and physical domains of QoL for men with prostate cancer actively receiving EBRT+ADT. It is not clear whether group-based or home-based exercise interventions provide better improvements, as neither of the two home-based studies recorded these outcomes. Our limited evidence thus far demonstrates that group-based interventions provide greater improvements in overall QoL and both types of intervention provide Level B evidence for reductions in fatigue.

The lack of recorded/ reported data on body composition, physical fitness and functional performance outcomes in home-based studies is also unexpected considering their importance in predicting overall QoL, metabolic syndrome and likelihood of fall- related fractures in this patient population, especially those patients also undergoing hormone therapy¹⁵. This is a clear gap in the literature.

2.3. Exercise Prescription Best Practice

Prescribing exercise to prostate cancer patients while they are undergoing EBRT+ADT is a relatively new approach to reduce CRF and improve HRQoL as demonstrated by the small number of studies in this review. A review of the literature makes clear that exercise training is ideally prescribed according to the FITT acronym³⁷, frequency, intensity, time and type.

- A. Frequency: the number of physical training sessions during a specified time period
- B. Intensity: the physiological effort associated with participation in that exercise
- C. Time: the duration of execution of a single session
- D. Type: the exercise modality e.g. Aerobic, resistance/strength

All four studies outline the expected *frequency, time and type* of exercise (table 6) but they do not provide a scientific justification for their chosen *exercise prescriptions*. The main weakness of all 4 studies is a failure to control for the key health benefit determining component of an exercise prescription; *intensity*.

Two of the review studies looked at a home-based aerobic intervention for prostate cancer patients, Truong³⁴ and Windsor³⁵. In Truong's study patients walked for 20 min/day, 3 days/week for 12 weeks whereas in Windsor's study patients walked for 30mins/day, 3days/week for each week of EBRT treatment. Neither author provides an explanation of why their exercise prescription is preferential for producing health benefits in this cohort of patients,

yet both authors agreed in their conclusions that their respective prescriptions reduced fatigue^{35,38} and improved HRQoL³⁸. We have no understanding of how intensely patients exercised. Controlling and evaluating intervention intensity is paramount, as the health benefits of the intervention are dependent on exercise intensity. For example, there is strong evidence from the American College of Sports Medicine recommendations for exercise interventions, the aforementioned Cochrane reviews, and home-based interventions of ADT-only prostate cancer patients - that the physical activity intensity needs to be mild to vigorous (MVPA) to have any health benefits i.e. improving patients HRQoL or fatigue³⁹. Considering the clear evidence for an intervention of MVPA intensity, what is an appropriate exercise prescription for prostate cancer patients undergoing RT+ADT?

The *frequency* and *time* and *type* of physical activity are easy to prescribe and measure in an intervention, however *intensity* is difficult. Evidence suggests that many people struggle to subjectively measure their exercise *intensity* after only hearing or reading a description of what it should feel like i.e. using the popular Borg scale of perceived self-exertion. Perceived exertion is an individual's subjective rating of exercise intensity, formed by assessing their body's physical signs such as heart rate, breathing rate and perspiration/sweating. Participants hear or read a description of how they should feel when engaged in moderate intensity physical activity (11-15 on the Borg scale or 60% to 80% of max effort).

The Irish national guideline of 150 min/week of MVPA is too abstract for most people to monitor and achieve. Participant potential difficulty in *subjectively* gauging exercise intensity presents a challenge in designing a home based walking intervention. We therefore need a valid, reliable and *objective* intensity monitoring tool that is affordable and easy to use. Accelerometers are perhaps the most common method of measuring physical activity directly in a laboratory setting but these monitors are prohibitively expensive and not validated for special populations such as the sample in the current research⁴⁰. The pedometer on the other hand is an objective activity monitoring tool which is affordable and more likely to be adopted for clinical and real world application⁴⁰.

2.3.1. The Pedometer: Measuring Exercise Intensity by Proxy

A pedometer tracks the volume of daily activity by measuring steps per day. Marshall *et al*⁴⁰ translated current recommendations for Moderate to Physical Activity (MVPA) into a pedometer- based step goal. Their evidence supports a public health recommendation/health promotion heuristic that walking at least **3000 steps in 30 minutes on 5 days each week, i.e. a cadence of 100 steps/minute and accumulated in minimally 10 minute episodes** be used to indicate the minimum value for MVPA⁴¹. This recommendation is based on research i.e. studies on adults that directly measured the number of steps and verified activity intensity in absolute terms of metabolic equivalents or METs (1 MET = 3.5 ml O₂/Kg/min or 1 Kcal/Kg/hour)⁴¹. To

be an accurate translation of public health guidelines these steps should be taken over and above *baseline levels of daily activity/background activity*, i.e. 15000 step/week at 100 steps/minute above baseline step/week.

2.3.2. How Many Steps Are Enough for Prostate Cancer Patients? -

Establishing Baseline Levels of Daily Activity/Habitual Steps/Day

Quantifying baseline level of non-exercise PA (habitual steps) is considered problematic as it has been influenced greatly by reduction of PA in most jobs, a reliance on labour-saving devices, passive transport and passive recreational activities⁴¹. Quantifying baseline levels of PA is further complicated in older adults, particularly those suffering from a chronic condition such as cancer, since self-reported walking activity increases with age in older adults while objectively monitored PA decreases⁴¹.

Tudor-Locke's *et al* review⁴² of 28 objectively monitored studies of adults ≥ 50 years of age reported that step-defined PA ranged from 2000 -9000 steps/day for this group. In a similar review of 60 studies of special populations including breast cancer patients Tudor Locke *et al*⁴³ reported that older adults with disabilities took the fewest steps/day (1214 steps/day) followed by COPD suffers (2237 steps/day). The highest number of steps/day were taken by Type 1 diabetes suffers (8008 steps/day). These broad ranges of steps/day reflect the natural diversity of abilities common to older adults and special populations especially given that not all chronic conditions impact physical mobility and/or endurance⁴¹.

There is little evidence to inform our views on baseline steps/day for prostate cancer patients undergoing RT+ADT. Tudor Locke *et al*, 2011⁴¹ identifies 10 pedometer based physical activity interventions involving cancer patients. Only one of these studies¹⁴ involved prostate cancer patients. It was a home-based intervention of the 19 patients in the intervention arm only 6 had prostate cancer and only one had or was currently receiving ADT. In the control arm 5 patients had prostate cancer and only 2 had or were currently receiving ADT. In this study, baseline steps/day for the control and intervention group were 5544 ± 2746 and 7222 ± 2691 respectively. Post-treatment steps/day were 4796 ± 2613 and 11200 ± 5851 . These figures represent a decrease in steps walked of 572 ± 2139 for the control group and an increase in steps walked of 3977 ± 5959 for the intervention group¹⁴.

Despite the limited similarities between the patient samples of the above study and the proposed study, it is encouraging to see the positive increase in daily steps in the intervention arm. These figures should be viewed with caution as it appears that baseline assessments of daily steps occurred after EBRT commenced and thus is not a true reflection of daily background steps/habitual steps. The process of being on treatment and the logistics involved may cause a natural increase or decrease in habitual steps/day. Consequently the success of the intervention may be inaccurate. The current study will control for this potential bias.

2.3.3. Calculating Exercise Prescription ExPx- Combining Habitual Activity with MVPA Prescription

Consider a prostate cancer patient with a background daily activity of 7222 steps/day as in Mustian et al¹⁴, determined by a pedometer. His tailored exercise prescription would be calculated as follows:

	MVPA days (steps)
Background daily activity	7222
MVPA (30min at 100 steps/min)	3000
Total	10222

The above table projects an estimated 10222 steps/day on the 5 days that include the goal of 30 minutes of MVPA. Over the course of a week this averages out to 9364 steps/day (7 days at 7222 added to 15000 MVPA steps).

Despite prescribing tailor- made exercise interventions and controlling for intensity, the efficacy of the intervention is dependent on what many authors consider to be the “Achilles heel” of exercise intervention RCTs- adherence

Getting people to Exercise-adherence- the Achilles heel of exercise RCTs⁴⁴

Adherence is defined by the World Health Organisation (WHO) as “*the extent to which a behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider⁴⁵*” More specifically, exercise adherence may be defined as the extent to which the intervention group perform the exercise prescription. Conversely, exercise contamination refers to the extent which the control group has performed the exercise prescription⁴⁶. The critical success determining components of RCT’s to test the efficacy of exercise interventions are high levels of exercise adherence in the intervention group and low levels of exercise contamination in the control group⁴⁶.

An insufficient investigation of exercise adherence and contamination is a key weakness of the four RCTs in this review. Only Truong *et al*³⁴ considered exercise adherence in the intervention group, although not fully. They reported a reported protocol adherence of 84% (42/50 patients) with positive observations in fatigue reduction and QoL increases. Disappointingly, the protocol defined adherence by frequency, time and type (FTT) but did not factor in adherence to a prescribed exercise intensity (I).

The speciality of Cardiology has the most experience in accessing adherence to exercise interventions. Only 20 years ago exercise was prescribed in an experimental setting, today it is

a Class 1 recommended non-pharmacological treatment for all stable heart failure patients³⁷. However, despite its class 1 recommendation, implementation in clinical practice is low³⁷.

The European society of Cardiology suggests that low clinical implementation is as a result of underwhelming results from large trials such as “Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training”. In this trial, 2331 patients were randomised to either aerobic exercise training or usual care to determine whether the intervention was able to reduce all-cause mortality/hospitalisation and improve QoL. While the results favoured the exercise intervention the effect size was less than expected. The authors conclude that the most likely explanation for these underwhelming results is the aforementioned “Achilles heel” of exercise training programmes that is non-adherence. Only 40% of patients in the exercise group reported weekly training volumes at or above those recommended. This is despite providing a supportive environment, a well-controlled RCT, formal education, activity logs, telephone contact, regular visits to the clinic, and heart rate monitors³⁷. Considering the importance of adherence in determining the efficacy of exercise interventions in RCTs, it is crucial to monitor and improve adherence in both the exercise and control group⁴⁴.

What do we know about getting cancer patients to exercise?

Most research on adherence has focused on cancer survivors after cancer treatment. A systematic review by Bourke et al⁴⁷ (2014) “Interventions for promoting habitual exercise in people living with and beyond cancer” reported that interventions to promote exercise in cancer survivors who report better levels of adherence share some common behaviour change techniques as defined by Michie et al⁴⁸ i.e. setting programme goals, prompting practise and self-monitoring and encouraging participants to attempt to generalise behaviours learned in supervised exercise environments to other, non-supervised contexts⁴⁷.

They also reiterate that prescriptions should be designed around individual capabilities, and frequency, duration and intensity or sets, repetitions, intensity or resistance training should be generated on this basis⁴⁷.

There is a gap in the literature regarding the adherence of patients receiving active cancer treatment who are likely to encounter disease and treatment-related side effects that might affect exercise behaviour⁴⁴. To obtain the maximum health benefits of the proposed home-based walking exercise intervention, every effort must be made to achieve 100% adherence to the FITT prescription in the intervention group and 0% contamination in the control group⁴⁶.

Shang *et al*⁴⁴ provide the most pertinent research to help us achieve this aim. Their RCT to test exercise intervention among patients with mixed cancer diagnoses and treatments, undergoing active treatment, reported how adherence significantly affected intervention efficacy. They analysed exercise-related adherence patterns and identified factors related to exercise adherence

in the intervention group and exercise contamination in the control group. Exercise non-adherence in the intervention group was 32% while the exercise contamination rate in the control group was 12%. Independent predictors of adherence for the exercise group were baseline level of physical fitness, and pre-treatment fatigue ($p < 0.01$, $p < 0.01$). Past exercise history significantly predicted exercise contamination ($p < 0.05$) in the control group⁴⁴. Considering this information, it seems pertinent to record these pre-treatment variables that are known to be significantly associated with fatigue and HRQoL⁴⁴ for potential use in a future confirmatory trial.

In addition to recording the above predictive factors, this study will incorporate the following evidence based behaviour change techniques;

- A. The home-based walking intervention will be prescribed according to the FITT ideal.
- B. Set programme goals (outcome), action planning, barrier identification, promote practise, encourage participants to attempt to generalise behaviours learned in supervised exercise environments to other, non-supervised contexts, provide instructions and how and where to perform the exercise, demonstrate the exercise, environment restructuring, and time management⁴⁸.
- C. Self-monitoring⁴⁸: i.e. the use of both subjective (log-books) and objective (pedometers) methods to assess adherence.
- D. Two baseline values of patient steps/day will be established. A “pre-treatment” and “on-treatment” value. This distinction will enable us to distinguish the natural reduction in daily steps walked by patients when they undergo EBRT, and to minimise bias in pre/post treatment steps/day calculations.
- E. Distinct from previous exercise intervention with cancer patients where the exercise was carried out before or after medical treatment, our intervention concerns only prostate cancer patients currently undergoing EBRT+ADT. This has several adherence promoting advantages as it enables us to monitor and encourage patients daily (as in a hospital based intervention) as they attend for treatment, while at the same time providing a pragmatic, low resource home-based intervention.

2.4. Conclusions From the Literature

There is strong evidence that patients with localised prostate cancer undergoing RT+ADT will experience clinically significant adverse side effects like decreased physical and functional capacity and fatigue which will diminish HRQoL and potentially increase the risk for coronary artery disease, stroke and type-2 diabetes. The public health burden of caring for prostate cancer survivors may therefore become even greater than caring for prostate cancer patients.

Despite current multimodal approaches to ameliorate CRF and HRQoL including patient education, pharmaceutical agents, aetiology-specific interventions, and non-pharmacological

therapies, patients in SLRON and other cancer centres continue to suffer from CRF and subsequent reductions in HRQoL. Considering the lack of effective treatments, RCTs are needed to confirm the feasibility and efficacy of the most promising solution; moderate to vigorous physical activity.

The literature on exercise interventions in men with prostate cancer undergoing RT+ADT represents less than 10% of all reported cancer related RCTs of exercise interventions. These RCTs have shown consistently that physically active prostate cancer patients have significantly greater QOL and less fatigue than those who are less active. The level A and B evidence for improvements in HRQoL and fatigue in these RCTs is consistent with both 2012 Cochrane reviews of exercise interventions for all cancer patients.

Many patients believe that an increase in physical activity would provide many benefits including symptom relief¹⁵. Despite this belief, and evidence supporting exercise interventions, prostate cancer patients' participation in physical activity is low. Some researchers consider that poor patient participation is a result of poor knowledge on the part of health professionals and subsequent lack of physical activity prescriptions^{15,49}.

No authors to date have dealt with the practical issues of RCT feasibility e.g. resources, management and processes. Greater HRQoL benefits for prostate cancer patients have thus far been associated with facility-, rather than home-based interventions⁵⁰. The cost and availability of human resources to provide exercise programs at radiotherapy centres is a barrier that severely limits programme delivery and access⁵⁰. This is particularly relevant in the Irish health system at present as it is under extraordinary financial pressure. In addition, the patient related obstacles of extra time spent in a hospital per day, extra parking costs and negative treatment experience may reduce participation in a facility-based intervention⁵⁰. Considering these potential barriers, a home-based intervention is the preferred option for maintenance of exercise adherence.

A home-based intervention is particularly appropriate for prostate cancer patients continuing ADT post treatment as the treatment and side effects may be experienced long term⁵⁰. The most recent literature by Santa-Mina *et al*⁵⁰ on ADT only patients provides further evidence in favour of both aerobic as opposed to resistance, and home- as opposed to facility-based exercise interventions for prostate cancer patients. In addition they suggest that aerobic exercise is more effective in stimulating long-term changes in exercise behaviour as patients are likely to be more familiar with AE such as walking than RE modalities⁵⁰.

The research to date has tended to focus on evaluating the efficacy of the exercise intervention but no study has controlled for the foremost health determining component of FITT exercise prescription "intensity" and the related Achilles heel³⁷ of exercise interventions "exercise

adherence”. The current research will prescribe tailored step/day based exercise prescriptions and measure adherence according to the best practice recommended FITT classification. To obtain the maximum benefit of the intervention we will employ objective pedometers and subjective logbooks to increase adherence in the intervention group and reduce contamination in the control group. Considering that,

- there are numerous hospital and patient financial and logistical disadvantages with supervised, facility-based group exercise interventions,
- aerobic and home-based interventions have demonstrated relatively strong evidence (Grade B) for improving HRQoL and reducing fatigue,
- prostate cancer patients may find it easier to maintain a simple walking regime than a new resistance programme in the long-term,
- exercise intensity is the most significant health benefit determining component of an exercise prescription
- exercise adherence is the weak link of previous exercise RCTs

there is a need to evaluate a pragmatic, tailored , moderate to vigorous intensity home-based aerobic exercise intervention for prostate cancer patients actively undergoing EBRT+ADT⁵¹ that encourages maximum adherence in the intervention group and minimum contamination in the control group.

3. METHODS

3.1. Pilot Study Objectives

There is a clear gap in the literature concerning the feasibility of a home based MVPA aerobic exercise intervention to reduce fatigue and increase HRQoL for patients with localised prostate cancer actively undergoing EBRT+ADT.

We hypothesise that in a proposed **future confirmatory study**, patients in Ireland and countries with similar treatment protocols, with localised prostate cancer undergoing radical EBRT+ADT randomised to the MVPA walking exercise intervention will experience less fatigue in comparison with the standard care control group over the period of radiotherapy treatment and at 1-month follow-up.

The objectives of this pilot study are categorised as follows:

1. **Process-** to assess the feasibility of the processes that are fundamental to the success of the main study.
2. **Resource-** to assess the time problems that may occur during the main study.
3. **Management-** to assess the potential human and data management problems.
4. **Scientific-** to assess intervention safety and estimate the interventions effect size on cancer related fatigue and its variance.

3.2. Pilot Study Endpoints

(See 3.7.3 for required feasibility criteria to proceed to a future confirmatory RCT at SLRON)

Table 8 below outlines the specific pilot study endpoints associated with each of this studies process, resources, management and scientific objectives.

Study objective	Endpoint
Process:	<ul style="list-style-type: none"> • Baseline characteristics distribution • Eligibility criteria acceptability • Recruitment rates • Refusal rates/willingness to be randomised • Retention rates • Schedule of assessment distribution • Study questionnaire acceptability • Study tools acceptability • Satisfaction due to intervention
Resources:	<ul style="list-style-type: none"> • Key process times • Room and equipment availability
Management:	<ul style="list-style-type: none"> • Pilot study management issues • Data entry issues • Potential new data value
Scientific:	<ul style="list-style-type: none"> • Is it safe to use the study’s exercise intervention? • Exercise prescription adherence rates in the intervention group and exercise contamination in the control group • Determine the impact of a home-base walking exercise intervention and its effect on fatigue <ul style="list-style-type: none"> ▪ What is the estimate of the treatment effect? ▪ What is the estimate of the variance of the treatment effect? • HRQoL, • Anthropometric measure and • Physical Performance <p>In patients with localised prostate cancer actively undergoing radical EBRT + ADT, and to use these data to assist in sample size estimates for a future confirmatory trial in an Irish setting.</p>

Table 8: Pilot Study Endpoints

3.2.1. Proposed Future Confirmatory Study Endpoints

Primary Endpoint

- Patient assessed fatigue

Secondary Endpoints

- Patient assessed HRQoL
- Anthropometric measurements
- Functional fitness measurements
- Rate of adherence/contamination to exercise intervention
- Patient satisfaction with exercise intervention

Intervention & control arm

Intervention arm only

3.3. Pilot Study Design

This pilot study is a comparative randomised trial designed to provide preliminary evidence on the clinical efficacy of our proposed exercise intervention. Also known as a “feasibility” or “Vanguard” study, it is designed to assess the safety of the intervention, recruitment potential, co-ordination of multicentre trial and to increase clinical experience with the exercise intervention². It is the best way to assess feasibility of a large, expensive full-scale study². Conducting this pilot study prior to the potential main study will enhance the likelihood of success of the main study in SLRON.

This study is a two-arm, pilot, randomised controlled trial (RCT) of a home-based walking intervention. It consists of an intervention arm, in which patients adhered to a walking program for 6 weeks of their EBRT treatment and a control arm in which patients followed the standard treatment for their disease.

A qualitative study was also nested within the RCT. After completion of the walking programme, participants in the intervention arm were invited to take part in an in-depth interview. The researcher endeavoured to uncover insights into barriers and facilitators for participation on the walking program. A saturation of information occurred at four patients. Considering no further interviews were justified. These insights will be used to aid the design of future patient–centric home-based exercise programs. Control group participants completed an exercise Knowledge, Attitude and Practices (KAP) questionnaire. The 3 trial co-ordinators (one at each centre) were also interviewed to gain an understanding of process, resource and trial management issues. This pilot study followed the CONSORT guidelines for reporting pilot studies.

3.4. Participant Flow

Men with localised prostate cancer receiving radical EBRT+ADT were identified from CT schedules at each of the 3 SLRON centres, screened for eligibility (Section 3.8) and consented according to ICH-GCP protocols by a designated Registrar/Consultant and Trial Co-ordinator with ICORG GCP certification. All participants underwent baseline assessments at their planning CT appointment before randomisation and commencing EBRT including:

Baseline assessments at planning CT appointment

- Self-report questionnaires (Brief Fatigue Inventory [BFI] and Functional Assessment of Cancer Therapy-Prostate [FACT-P])
- Functional fitness (2 minute step test and 30 second chair-stand test)
- Anthropometric measures (Height, weight, % , waist circumference, body fat, % muscle/bone mass)
- Habitual/background steps/week measured using a pedometer given to patients at CT (A)

Randomisation during week 2 of EBRT

After completing all baseline assessments patients were randomised centrally by the CTRU administrator using a randomisation scheme with blocks of four to a home-based walking program (intervention arm) or to follow standard treatment (control arm).

Intervention arm:

Starting in week two of EBRT, participants randomised to the intervention arm were given a tailored step/day target. Participants were also asked to walk for a minimum of **3000 steps/day, in 30 min sessions (duration), 5 times/week (frequency) at a rate of 100 steps/minute (MVPA intensity)**. In other words patients were asked to achieve 15000 steps/week measured using a pedometer in 150 minutes in total. The minimum time allowed per session was 10 minutes. These 15000 MVPA steps were in addition to continuing to achieve their baseline steps/week (A below).

Calculating individual exercise prescriptions ExPx- combining habitual activity with MVPA prescription

Consider a prostate cancer patient with a background daily activity of 7222 steps/day as in Mustian et al¹⁴, determined by a pedometer. His tailored exercise prescription on each of the 5 MVPA days would be calculated as

The table to the right projects an estimated 10222 steps/day on the 5 days that include the goal of 30 minutes of MVPA and 7222 steps/day on the other 2 days. Over the course of a week this averages out to 9364 steps/day (7 days at 7222 added to 15000 MVPA steps).

	MVPA days (steps)
Background daily activity (A)	7222
MVPA Px (30min at 100 steps/min)	3000
Total	10222

Week	-2 (CT) → -1	-1 → Start EBRT → +1	+1 → +7
Pedometer Steps/week	Disregard (hawthorn effect)	Background steps (A)	Natural decrease due to EBRT
			Intervention → Ex Px (A + 15000 MVPA steps/week) Control → usual care

Participants were asked to continue with this programme throughout the course of their EBRT. The clinical research co-ordinator explained the home-based exercise program to the participants. To help improve adherence, a behavioural component exploring with patients how they could incorporate walking within their daily lives was carried out by the trial coordinator*. Patients were asked to fill in a log book to record the frequency, duration, and steps achieved for the 30 min MVPA intervention each day. Patients completed an exercise satisfaction questionnaire at 4 weeks (Mid EBRT), 7-8 weeks (End EBRT/post intervention) and at 1 month

follow-up. Four patients were also invited to take part in an in-depth interview after completion of the exercise intervention.

***Behavioural Component**

The Trial co-ordinator (TC) explored the intervention design with participants to promote adherence. This involved

1. Setting programme goals: TC's explained the individualised pedometer step target. As with all well-designed exercise programmes in any context, the exercise prescription (ExPx) was designed around the individual's capabilities, and exercise frequency, duration and intensity. A balance between a safe yet effective exercise intervention⁴⁷ can be achieved using these essential metrics of exercise prescription
2. Prompting practise and self-monitoring: TC'S walked with the participant at a cadence of 100 steps/min to enable the patient to experience what MVPA felt like. In addition TC's thoroughly explained how to monitor MVPA and regular steps on the pedometer.
3. Encouraging participants to attempt to generalise behaviours learned in the supervised exercise environment at randomisation to other, non-supervised contexts: i.e. exploring when and how the participant would fit their walking prescription into their daily schedule.

Control arm:

Patients randomised to the control arm were asked not to join any new formal physical exercise program during the study intervention period. Participants wore a sealed pedometer. Control group participants also completed a short exercise KAP questionnaire upon completion at 1 month follow up appointment.

All patients were reminded to wear their pedometer each day by treating radiotherapists and reminded again by the trial co-ordinator at weekly assessment clinics (standard care).

Follow-up schedule for all patients

4 weeks (Mid EBRT)

Repeat baseline assessments

7-8 weeks (End EBRT/post intervention)

Repeat baseline assessments

1 month Follow-up

Repeat baseline assessments

Thereafter patients continued with standard follow-ups as determined by their treating Radiation Oncologist. The Clinical Research Co-ordinator collected all the self-reported questionnaires and carried out the objective test of functional fitness and anthropometric measures. The 3 trial co-ordinators were interviewed upon completion of recruitment and all assessments to gain an understanding of process, resource and trial management issues

3.5. Outcome Measurement

1. Trial case report form (appendix A)

This form captured each patient's relevant medical history, disease characteristics, demographics and baseline and acute toxicities.

2. Fatigue: (appendix B)

To evaluate trends in fatigue, subjects in the control and exercise group were administered the Brief Fatigue inventory (BFI), a validated, self-complete fatigue assessment tool with 9 questions to quantify the presence and severity of fatigue, and the interference of fatigue on function and QoL. The QoL domains in the BFI are general activity, mood, walking ability, normal work or daily chores, relations with others, and enjoyment of life. Each question required participants' ratings from 0-10, with 0 indicating no fatigue and 10 indicating worst fatigue or interference. The maximum score is 90.

3. HRQoL: (appendix C)

To evaluate trends in Disease-specific HRQOL, subjects in the control and exercise group were administered the Functional Assessment of Cancer Treatment-Prostate (FACT-P). The minimal clinically important differences (MCID) on the FACT-P is 5.5. This instrument included 27 general questions that provide assessments of physical, social or family, emotional, and functional well-being. It also included 12 questions that queried "additional concerns" specific to prostate cancer and its treatment. The FACT-P has demonstrated construct validity and sensitivity and a test-retest reliability of 0.83. The maximum score is 156.

4. Physical Performance:

- A. **Cardiorespiratory Fitness:** 2-Minute Step Test, the number of full steps completed in 2 minutes, raising each knee to a point midway between the patella (kneecap) and iliac crest (top hip bone) was recorded. Score is number of times each knee reaches the required height.
- B. **Functional Fitness:** 30-Second Chair Stand test, measured the number of full stands that could be completed in 30 seconds without using arms for help.

5. Logbook: (appendix D)

To assess adherence to individualised exercise prescriptions, participants were asked to record the frequency and duration of each 30 minute session of MVPA. This was cross checked with daily and weekly step counts as recorded on participants' pedometers.

6. Patient acceptance of exercise intervention: (appendix E)

This was evaluated using a self-reported questionnaire designed to elicit information on intervention participants' attitude to, satisfaction with and convenience of the exercise program.

7. Insights into acceptance and adherence: (appendix F)

Post intervention, insights into acceptance and adherence of the exercise intervention was explored utilising in-depth interviews. An interview guide was employed to probe into possible barriers and facilitators to MVPA in the intervention group.

8. Process, resource and trial management insights. (appendix H)

A key informant interview with each trial co-ordinator in each of the three SLRON centres was conducted post trial.

9. An on-line screening and recruitment log was maintained.

10. Control Group, physical activity Knowledge Attitude and Practices questionnaire.

This questionnaire was administered to control group participants at 1 month follow up appointments. (appendix I)

3.6. Table of Assessments

Table 9 below outlines the range of assessments and assessment schedule of intervention and control group participants.

Investigations		Baseline	Mid EBRT	Last week/End EBRT	1m FU
All PARTICIPANTS					
On study case report form (Appendix A)	Age, partnered status, job status, education ,relevant med history, baseline and weekly treatment toxicities	x			
Steps/day (Pedometer)	From 2 weeks before commencing EBRT (CT scan) until end of EBRT				
Anthropometric measures Including Bioelectric Impedance <i>(italicised assessment)</i>	Height, weight, % <i>body fat/muscle mass</i> , waist circumference, <i>bone mass</i>	x	x	x	x
Physical Performance	A. 2 minute step test B. 30 second sit-stand test	x	x	x	x
HRQoL	Functional Assessment of Cancer Therapy-Prostate (FACT-P)	x	x	x	x
Fatigue	Brief Fatigue Inventory (BFI)	x	x	x	x
Exercise intervention. 3000 steps in 30 min sessions (duration), 5 times per week (frequency) at a MVPA intensity of 100 steps/min. Sessions should last a minimum of 10 minutes i.e. 3 x10 minute sessions on MVPA days. These steps will be in addition to usual habitual steps as determined at baseline.					
INTERVENTION ARM ONLY					
Behaviour Change Section (sec 3.4)	Explore common behaviour techniques	After randomisation Goal setting, Prompting practise and self-monitoring etc.			
Adherence	Patient log book <i>Frequency and duration of MVPA walking. Steps/day</i>	Completed after each walk			
Understanding acceptance and adherence	In-depth interviews of 4 intervention arm participants –using interview guide - <i>barriers and facilitators</i> ,			x	
Exercise satisfaction questionnaire	Self-reported questionnaire evaluating attitude, tolerance and satisfaction with walking programme			x	
CONTROL ARM ONLY					
Exercise Knowledge attitude and practices	Self-reported questionnaire KAPs of exercise during their EBRT			x	

Table 9: Pilot Study Assessment Schedule

3.7. Statistical Approach and Sample Size for Pilot and Main Study

3.7.1. Pilot Study

The target population for this study were men who received EBRT+ADT in the SLRON. Potentially eligible patients were identified from CT schedules. The first 24 eligible patients to consent constituted the study sample. Sample selection was based on the same intended inclusion and exclusion criteria as the main study. The sample used in the pilot study may be included in the main study, provided that the researcher can preserve key features of the proposed main study in the pilot². When pooling of pilot and main study data is done properly it can increase the efficiency of the main study².

Patients were recruited from the three centres which constitute the SLRON. The network is designed so that each patient receives identical treatment irrespective of treatment centre. Staff are trained and work using the same network standard operating procedures. Clustering of data was therefore not an issue.

For pilot studies the recommendation is a sample size of 12 per group⁵². This sample size was considered large enough to provide useful information about the aspects of the pilot study that were being assessed for feasibility.

This pilot study provided estimates of the mean fatigue in the control group and the standard deviation in each group in order to inform the sample size calculation for a future confirmatory RCT. At present we do not have any data on fatigue levels of Irish cancer patients receiving EBRT+ADT. Chang *et al*⁵³ found that the BFI “usual” fatigue mean score was 5.0 (± 2.42) and BFI “worst” fatigue was 5.7 (± 2.5) for cancer patients. Mendoza *et al*⁵⁴. (1999) found that the BFI “worst” fatigue mean score was 4.7 (± 2.8) for cancer patients and 2.2 (± 1.8) for controls ($p < 0.01$).

3.7.2. Main Study

To increase the efficiency of the main study, the sample used in the pilot study will be included in the main study. The key features of the main study were preserved in the pilot study and no potential bias is envisaged due to multiple testing or opportunistic actions since the pilot study is not using statistical tests.

In the main study, the mean fatigue for the two groups of patients will be compared using a two-sample t-test at the 5% significance level.

Sample size estimates for the main study are based on combinations of (i) differences in usual fatigue ranging from a minimum clinically important difference of 1 to a difference of 2 and (ii) variability estimates of 2.2 to 2.8. Sample size estimates based on 80% statistical power to detect these differences between control and treatment groups using a two-tail two-sample t-test using a 5% significance level are presented in Table 10.

Underlying Variability	Mean difference between Control and Test groups			
	1.0	1.4	1.8	2.0
2.2	77	40	25	21
2.3	85	44	27	22
2.4	92	48	29	24
2.5	100	52	32	26
2.6		56	34	28
2.7		60	37	30
2.8		64	39	32

Table 10: Future RCT Sample Size Estimate per Arm*

*For 80% Statistical Power (assuming variability is equal in each group)

Table 10 suggests that the numbers required to detect a minimum clinically important difference of 1 with a standard deviation of 2.6 or greater are impractical i.e. it would not be feasible to recruit such large numbers of patients. For the main study evaluable patients are defined as those for whom BFI at one month post RT is documented, as the primary endpoint is to show that fatigue as measured on the BFI scale is less at this time point in the intervention group.

3.7.3. Feasibility Criteria

The criteria below must be achieved in the pilot study at SLRON to recommend a future confirmatory RCT as feasible:

1. At least 50% of all eligible patients are recruited
2. A recruitment rate of 1 patient per centre per month
3. Complete follow-up in at least 70% of all recruited patients
4. ≤ 3 intervention related adverse events as specified by the study's lead Clinician.
5. 66% of the intervention group achieve an individual adherence rate of 66%
6. Encouraging fatigue trends in the intervention arm

3.7.4. Calculating Exercise Prescription Adherence/Contamination

A. **Exercise Adherent (EA)** \longrightarrow \geq Individual Adherence Rate (IAR) of 66%

B. **Individual Adherence Rate (IAR)** $= \frac{\text{Adherent Weeks (AW)}}{\# \text{ prescribed Ex Weeks}} = \frac{x}{7}$

C. **Adherent Weeks (AW)**

Exercise is prescribed according to Frequency, Intensity, Time and Type (FITT) and best practice is to measure adherence using the same criteria³⁷. For a participant to achieve an Adherent Week (AW) they must fulfil the following criteria:

- a. Frequency (F); \geq 66% of prescribed exercise sessions.
- b. Intensity (I); \geq 66% of prescribed step/week target i.e. \geq 66% of their baseline steps + (\geq 66% of 15000) steps
- c. Time (T); \geq 66% of prescribed time i.e. \geq 66% of 150 minutes = at least 100 minutes
- d. Type (T): Walking.

Similarly, exercise non-adherence or contamination in the control group was calculated by analysing steps/week. If a control group participant achieves their baseline steps + (\geq 66% of 15000 steps in any week they will be deemed non-adherent.

3.8. Participants' - Selection and Recruitment

All men with non-metastatic prostate cancer, booked for radical EBRT+ADT in the SLRON were screened for eligibility. Potential patients were screened prior to their planning CT scan. If deemed eligible, the clinical trial coordinator liaised with the patient's Consultant to get permission to approach the patient at CT. Potential patients were provided with full written information (participation information leaflet and consent form) (Appendix G) on the details of the research study and deemed fit to take part in an exercise intervention by a Medical Doctor, prior to consent. Participants were consented according to ICH-GCP guidelines. A study screening and recruitment log was maintained by the study co-ordinator at each site, on a central share drive at SLRON.

3.8.1. Inclusion Criteria

1. Pathologically confirmed non-metastatic prostate cancer.
2. Candidate for radical EBRT+ADT defined as curative intent treatment targeting the prostate or pelvis and prostate, fractionated once daily over 6-8 weeks.
3. ADT for \leq 1 year at 1 month Follow up.
4. At least 30 scheduled radiation treatments (6 weeks).
5. Sedentary lifestyle (no regular exercise, i.e. engaging in purposeful exercise or physical activity of moderate to vigorous intensity of 30 minutes or more, 3 times per week.)

6. Patient has read the participant information leaflet and signed the consent form.

3.8.2. Exclusion Criteria

1. Recurrent disease
2. Contraindications prohibiting participation in a moderate intensity walking program as determined by the patient's Radiation Oncologist or designated Registrar
3. Inability to perform written consent.

3.9. Participants Safety Risks, And Benefits

Participants' Consultant and General Practitioners were informed that their patients were taking part in this study. Participants were monitored during and after the study according to the same standard clinical guidelines as those choosing not to participate in the study. All participants underwent assessments at baseline, mid-EBRT, end of EBRT and at 4 week post-EBRT. Participants randomised to the exercise arm followed an individualised MVPA walking exercise prescription.

Patients were monitored at their normal scheduled on-treatment check-ups by their Consultant and/or his/her team of doctors. The team watched patients closely to see if they had treatment-related side effects. Patients were given a physical exam by their Oncologist prior to consent (standard practise) to ensure that they are healthy enough to participate in a walking program. There was a small risk (less than 1%) that a patient could receive muscular injuries from the walking regimen. There was also a small risk (less than 1%) that a patient may have suffered from heart problems due to increased exercise, but this risk was no greater than for the general public.

Before consent patients were informed that there may or may not be direct benefits for participants. Participants in the intervention arm may benefit from increased physical fitness because of the walking exercise program. Participants may or may not experience reduced fatigue resulting from participation.

3.10. Administrative Responsibilities

3.10.1. Data Management

3.10.1.1. Media of Controlled Data

Paper based data (questionnaires) were collected in this study and results entered into a computerised database. Individual in-depth interviews with the intervention group post intervention were recorded (Audio).

Medical records were accessed as they were integral to the study. Patient characteristics, disease characteristics, and follow-up information were important for the assessment of the study objectives.

3.10.1.2. Data Access and Storage

Consent to analyse the data was sought as part of the consent process outlined above. Only the study team had access to collected data. All data collected was analysed retrospectively and anonymously at the end of the study. Individual patients were offered the option of being informed of the study results. Data was coded and the trial coordinator retained the key to re-identify the data.

All data collected during the course of this research was stored on the trial coordinator's password protected PC in the Clinical Trials Unit, St Luke's Hospital Rathgar.

Paper based data questionnaires were destroyed after being transferred to the electronic version using the shredding facilities provided by St Luke's Hospital. The shredded paper was collected and recycled. Electronic data will be retained for a fixed period of 5 years at SLRON.

3.10.1.3. Confidentiality

The Principal Investigator is the only person with a key to the identity of the research participants. The named investigators had access to anonymised data and each patient's study number. The key linking patient identity to study number was destroyed once all required follow-up information had been acquired so that only irrevocably anonymous data are retained.

3.11. Good Clinical Practice

The study was conducted in accordance with the EU Directive 2001/20/EC and International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate ethical requirement(s). The investigator was thoroughly familiar with the appropriate use of the study treatment as described in the protocol. Essential clinical documents were maintained to demonstrate the validity of the study and the integrity of the data collected. Master files were established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

3.12. Ethical Considerations

The study was conducted in accordance with ethical principles founded in the Declaration of Helsinki (Appendix J). The SLRON (21st March 2013 and 18th February 2014) and The London School of Hygiene and Tropical Medicine (LSHTM) (4th February 2014) ethics committees

reviewed all study documentation in order to safeguard the rights, safety and well-being of the patients. The study was only conducted at sites where full approval had been obtained.

3.13. Patient Information and Informed Consent

After the study was fully explained, written informed consent was obtained from the patient prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent complied with ICH-GCP and all applicable regulatory requirements. The network also provides a range of allied health services at each site which are available to all patients, including counselling, psycho-oncology and physiotherapy. Study participants can avail of such services for the duration of their treatment/trial and while in follow up.

3.14. Patient Confidentiality

In order to maintain patient privacy, all case report forms, study reports and communications identified the patient by initials and the assigned trial number.

3.15. Protocol Compliance

The investigator conducted the study in compliance with the approved protocol (V 4.0). No changes to the protocol were required during the study.

3.16. Project Organisation and Logistics

This study was conducted in collaboration with the St Luke's Radiation Oncology Network of cancer centres in Dublin, Ireland. As Principal Investigator, Ciarán Doyle had the overall responsibility for this research project. His academic supervisors: Dr Val Curtis, Dr Wolf-Peter Schmidt, Dr Alison Tree, Mary Dunne and Dr Pierre Thirion provided scientific and methodological guidance. The co-investigators at SLRON contributed to data analysis and the write-up of the results and conclusion.

3.17. Communication Research Results

The pilot study results will be reported using the CONSORT format and were presented in a report to the SLRON. It is planned to present the study findings at an appropriate conference, and to publish them in a suitable journal. Finally the study will be presented in partial fulfilment of a "Doctor of Public Health" thesis at the London School of Hygiene and Tropical Medicine. As part of the consent process, patients will be asked if they would like to be informed of the study results when they become available.

4. RESULTS

4.1. Process

This section assesses the feasibility of the processes that are crucial to the success of the main study. The results in this section come from a combination of quantitative and qualitative data collection methods.

4.1.1. Consort Flow Diagram

Figure 6 below is a Consort flow diagram of the progress through the phases of this randomised trial (that is, enrolment, intervention allocation, follow-up, and data analysis).

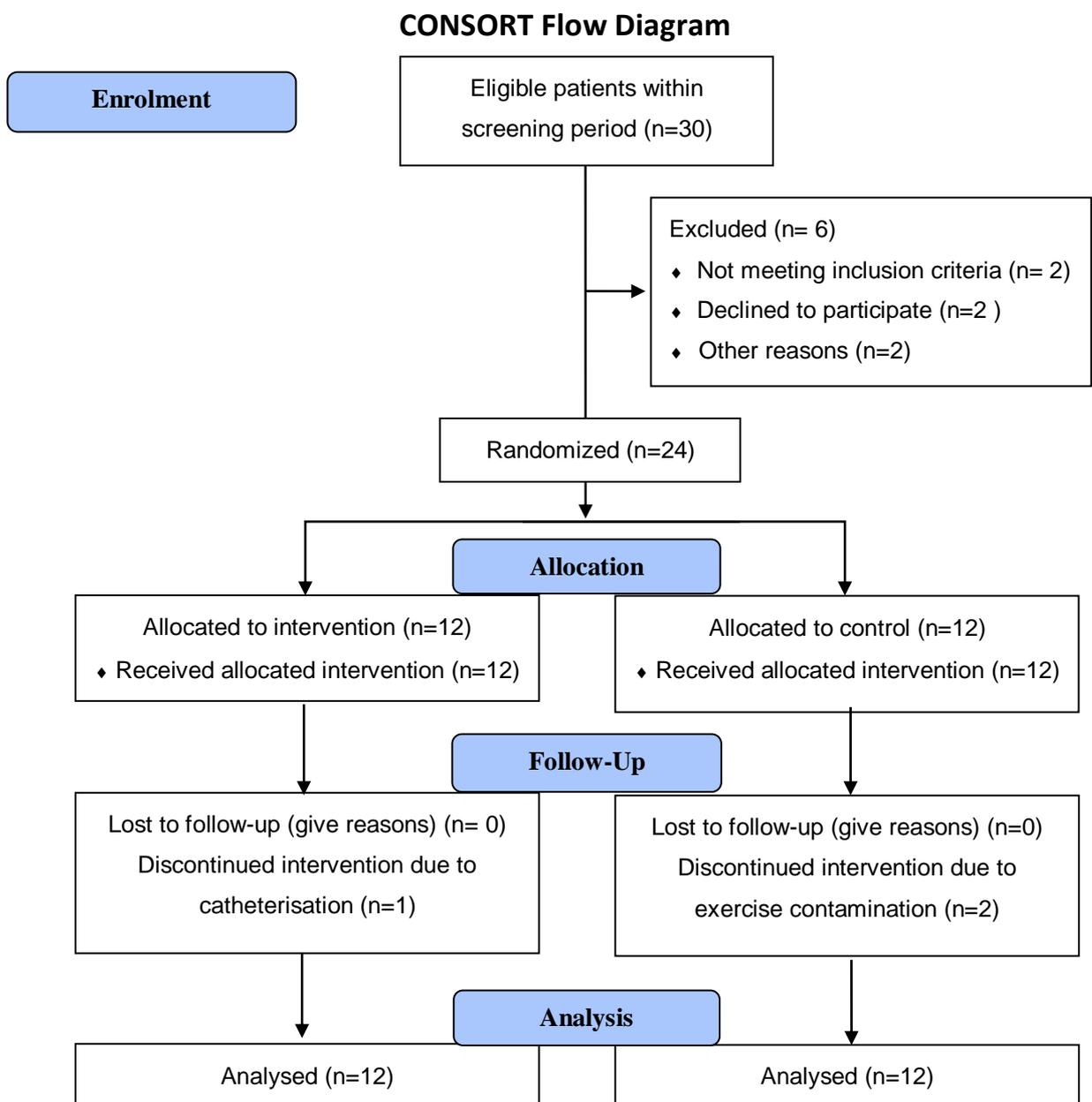


Figure 6: Consort Flow Diagram

4.1.2. Baseline Characteristics

The distribution of anthropometric measures, time since diagnosis, baseline steps per day, functional fitness, age, T-stage, risk group, EBRT, ADT and social characteristics were similar in the intervention and control groups. The only major differences were that the intervention group had more smokers and less drinkers than the control group. Intervention group participants were more fatigued but reported a greater HRQoL than control group participants' pre randomisation. (Table 11)

Variables	Intervention (n=12)		Control (n=12)	
	Mean	SD	Mean	SD
Anthropometric Measures				
Age (yr)	66	5.4	65.1	6.5
Height (cm)	169.5	9.6	174.8	4.7
Weight (kg)	82.5	18.8	84.2	9.8
% Body fat	28.5	6.8	26.7	4.1
% Muscle mass	68.3	6.5	69.5	3.9
Bone mass (kg)	2.9	0.4	3.1	0.3
Waist circumference (cm)	105.5	15.4	107.6	11.2
Time since PCa diagnosis (mts)				
	8.6	6.5	8.1	3.4
Habitual steps per week				
	45400.7	17751.9	42043.2	18185.8
Functional Fitness				
2-min step test	150.5	62.8	147.6	46.9
30 sec sit-stand test	15.7	6	15.4	4.3
Fatigue (BFI) (0-90)				
	22.2	17.6	13.4	10.7
HRQoL (FACT-P) (0-156)				
	126.7	19	126	15.5
Referring PSA				
	9.9	5.8	14	22.8
Gleason score (%)				
7		4 (33.3)		7 (58.3)
>7		6 (50)		5 (41.7)
T-stage (%)				
T1		2 (16.7)		3 (25)
T2		4 (33.3)		4 (33.3)
T3,4		6 (50)		5 (41.7)
DRE (%)				
Not assessed		2 (16.7)		0
T1		4 (33.3)		4 (33.3)
T2		3 (25)		6 (50)
T3		3 (25)		2 (16.7)
Risk category (%)				
Intermediate risk		4 (33.3)		5 (41.7)
High risk		8 (66.7)		7 (58.3)
Pre baseline ADT duration (%)				
ADT (0-6mts)		2 (16.7)		2 (16.7)
ADT (3-6mts)		8 (66.7)		9 (75)
ADT (6-9mts)		2 (16.7)		0
ADT (9-12mts)		0		1 (8.3)
Expected ADT duration (mts)				
LHRH	13.8	13.5	16	14.8
Bical	7.5	9.2	7.8	9.1
LHRH type (%)				

Decapeptyl	7 (58.3)			7 (58.3)	
Eligard	4 (33.3)			3 (25)	
Degarelix	1 (8.3)			0	
Prostap	0			2 (16.7)	
Anti-Androgen type (%)					
Casodex	11 (91.7)			12 (100)	
None	1 (8.3)			0	
Co morbidities (%)					
Hypercholesterolemia	4 (33.3)			5 (41.7)	
Hypertension	5 (41.7)			7 (58.3)	
Diabetes	2 (16.7)			0	
Current Smoker (%)					
Pack years	13	4 (33)	14.4	20	18.5
Current drinker (%)					
Units per week	15.9	6 (50)	19.3	32.7	33.3
Family Hx (%)					
Yes		6 (50)		4 (33.3)	
No		6 (50)		8 (66.7)	
Marital status (%)					
Married		9 (75)		8 (66.7)	
Partner		2 (16.7)		0	
Other		1 (8.3)		4 (33.3)	
Employment status (%)					
Employed		2 (16.7)		3 (25)	
Unemployed		2 (16.7)		1 (8.3)	
Retired		8 (66.7)		8 (66.7)	
Education (highest) (%)					
Primary		1 (8.3)		3 (25)	
Secondary		9 (75)		7 (58.3)	
Tertiary		2 (16.7)		2 (16.7)	
ADT = androgen deprivation therapy BFI= brief fatigue inventory DRE= digital rectal exam					
FACT-P = functional assessment of cancer therapy-prostate LHRH = Luteinizing Hormone Releasing Hormone SD = standard deviation					

Table 11: Participants Baseline Characteristics

4.1.3. Eligibility Criteria Acceptability

TCs reported no issue determining and recruiting eligible patients for this pilot study. One TC reported: *“I found it very easy to read and, so, easy to understand. It was laid out very clearly. It was very clear on which patients were allowed to be recruited into the study and it was clear on what patients were not suitable. I didn’t find it restrictive at all⁵⁵”*. Another TC corroborated this point *“I found the criteria pretty good. We got almost all our prostate patients who were on hormones onto the trial. That was very good. Very few patients were coming through with mobility issues, things that would make it unsafe for walking. So that was good to have that in it. Otherwise I didn’t see any reason to exclude other patients that fitted the treatment criteria⁵⁶”*

One TC suggested that we should recruit patients at an earlier point in their treatment:

“There is definitely enough information at CT to recruit patients in this centre. However, due to the nature of the study, I think it would be ideal if patients were recruited at an earlier stage... I think when their hormone prescription is being written and given to the patient, I think that would be a better time so that if there is an impact of the study on weight loss that that is

encompassed at the CT scan and when they go ahead for treatment... A true baseline, yes, when they start treatment, because we did see patients on treatment, their contour changing towards the end of radiotherapy, which is very positive for the intervention. On a larger study it might be great to have that effect at the CT scan so it is more true for the patient... I think it would not be feasible to do the assessment in an outpatients clinic, not at all. The assessment itself would not be feasible, it would nearly need to be a separate appointment if that was the case... I would be very reluctant to delay the start of hormone treatment but I would be very keen to start the exercise intervention in advance of CT. They'd be the two things I'd be trying to match up⁵⁶

4.1.4. Recruitment Rates

From 24/2/14 to 7/4/14, 28 eligible patients were approached for recruitment, 24 patients accepted. This represents a recruitment rate of 86% and an average recruitment rate of 4 patients per week. No patients were recruited in St Luke's Hospital as SLRON treatment booking policy over this period dictated that prostate patients be treated in either Beaumont or St James's centres. 17 patients were recruited in St James's hospital and 7 in Beaumont Hospital.

4.1.5. Refusal Rates

Only two eligible patients refused to participate in the study i.e. 7%. A participant in screening week three suffered from anxiety and decided that the intervention would be "too much" for him. The other patient in screening week four was "not interested in anything extra" on top of his standard treatment.

4.1.6. Retention Rates

The retention rate was 96%. One patient in the intervention arm had to withdraw from the study as he had grade 3 urinary pain and retention. This resulted in him needing a supra pubic catheter, that made it too uncomfortable for him to walk. This patient was assessed and followed up as per protocol.

4.1.7. Schedule of Assessments

The schedule of assessments (Table 12) appears evenly distributed between groups. Participants were assessed at roughly the same fractionation and days between assessments in each group.

Variables	Intervention (n=12)		Control (n=12)	
	Mean	SD	Mean	SD
	Fractionation		Fractionation	
Total #s	38.9	3.6	37.7	3.7
Randomisation (R) #	6.5	1.2	6.9	1.8
Mid EBRT ass #	21.2	2.3	20.4	2.4
End EBRT ass #	36.8	4.0	36.1	3.9
	Days		Days	
BL-R	23.6	2.6	24.9	3.5
BL-Mid	46.3	4.5	45.7	4.1
BL- End	69.8	6.1	69.8	6.8
BL-1mt FU	99.6	10.9	97.5	7.0
R-Mid	22.8	3.1	20.8	2.8
R-Mid #s	14.8	2.0	13.5	2.0
R-End	46.2	5.8	44.9	7.8
R-End #s	30.3	4.6	29.2	4.7
R-last#/Intervention duration (days)	49.6	4.9	47.7	8.2
R#-last#/Intervention duration #s	32.5	4.1	30.8	4.8
R-1 Mt-FU	76.0	10.3	72.6	7.8
Mid-End	23.4	7.4	24.2	6.6
Mid-1mt FU	53.3	11.7	51.8	6.6
End-1 Mt Fu	29.8	6.3	27.7	0.7
Last#-1mt FU	26.3	7.1	24.9	2.4

= "fraction" e.g. #7 is patients 7th treatment

BL= Baseline assessment

Mid = Mid EBRT assessment

End = End of EBRT assessment

1 mt Fu = 1 month FU assessment

Table 12: Distribution of Trial Assessments

4.1.8. Study Questionnaires Acceptability

TCs had no issues administering the main study questionnaires (BFI and FACT-P) to all participants or the exercise KAP questionnaire to the control group.

“I found both of them fine. I have a lot of experience of administering questionnaires, quality of life questionnaires, things like that. There was no problem; they are very similar to other quality of life questionnaires. The questions were very familiar; the format was very familiar, so due to my familiarity I found it very simple. I think most trial coordinators would use questionnaires so I can’t imagine anyone having difficulty with that⁵⁶.”

“The questionnaires were fine. I thought they were of a reasonable length, not too long or conversely short. I suppose patients find filling out questionnaires monotonous but I think there would be no benefit to changing the questionnaires to resolve that⁵⁷.”

TC also explained how study participants responded to the questionnaires. When given the option to self-complete or have the questionnaires read to them, in all cases patients chose the latter. This is common among trial patients in the SLRON network as explained by the TC⁵⁶ below:

R: In general I found that a lot of them liked to have the questions read out to them and shown to them. I: How does that compare to other studies we have? Is it unusual? R: Yes, it is. For this study, your study here, a lot of the fellas would have had poor eyesight, not reading difficulties but poor eyesight, with small print. It’s all very unfamiliar so they would say, ‘Would you just read it out, it’s easier’. And I have found the same with two palliative trials. I: So you think it is the patient population, as they are usually gentlemen in their sixties, that is the reason they prefer to have the questions read out to them? R: I don’t know. I wouldn’t pigeon-hole them as much as that because much older patients and much more sick patients of both genders I find very similar. I think in general maybe they just like to be talked to, maybe it makes it less like a formal exam. I don’t know. But even in the DCIS, which is more younger females, some of them will want you to read them out, some don’t. I: Because the questionnaires, both of them, are designed that they can be self-administered or they can be administered through a coordinator. R: Yes. I: Do you think it is good to have the option or just have all coordinators ask the questions? R: I think it is good to have the option. For two reasons: some patients will have reading difficulties and they will want you to read it out but, conversely, some of the questions are very personal, very sensitive topics are addressed and some patients will want to do that themselves and not have it spoken out, particularly if the patient is accompanied by a family member or a friend they don’t want knowing all the answers to the questions. I think it is great because you can still provide them with privacy while not isolating them from their family members.

Another TC explained that:

“They (participants) didn’t seem to have any issues once you took the time to explain what they were for and explained that it was their own opinion⁵⁵.”

4.1.9. Study Tools Acceptability

4.1.9.1. Log Book

TCs had mixed experiences administering the log books to intervention patients:

“I found the log book very straightforward but I found patients got really confused by the whole thing. It took a few times of explaining to them and which number to write in which box and

when but, in general, once they got it, they got it. I found very few people coming back having done it wrong⁵⁶.” Another TC had no such issues: “No, that was very clear. Again, once everything was explained thoroughly to them at the beginning, they seemed to get a good handle on it and it seemed to work out well⁵⁵.”

4.1.9.2. Body Composition Monitor

The bioelectric impedance scales proved problem free. One TC reported that:

“The Tanita scales that we have here, the little stand-on one, I found that very straightforward to use. I just used it under the guest profile, I didn’t save any of the profiles, but it was fine. Patients were able to get on it, no one every fell, there were no problems there. Tape measure, obviously measuring the circumference of the waist, was very straightforward⁵⁶.” Another TC agreed with this sentiment: *“the scales was very easy to use. It was very simple with very clear instructions to use it⁵⁵.”*

4.1.9.3. Pedometer

TCs had contrasting views on the pedometers, for example:

“No, no issues came up, which was great and I think the fact that they didn’t have to actually do anything with the pedometer was the main benefit of it, otherwise, you may run into problems. It turned out very well⁵⁵.”

In addition one TC was concerned with the user friendliness and quality of the pedometers:

“You would need a lot more pedometers and, if possible more user-friendly pedometers and ones that were easier to use and maybe more reliable. There was an odd one. The string broke on one; one of them got wiped one day, we’re not sure why. There are a couple of little issues with them that, even though they said when we bought them the spec was quite high and they were quite expensive for clinical trial purposes, in reality when they were tried and tested they weren’t quite as good quality as we were expecting... my biggest requirement would be ones that aren’t affected by mobile phone signals because, no matter how many times you tell patients...⁵⁶”

4.1.10. Potential Future Process Issues for a Future Confirmatory RCT

TCs were in agreement that the existence of this pilot study will eliminate a lot of the usual process issues that SLRON encounter with new RCTs. For example when asked the following question:

I: Do you think this feasibility study will make the process of rolling out a future confirmatory randomised control trial easier?

R: Oh yes, definitely. I think especially for the trial coordinators it is not a new thing to them so they are very familiar with the workings of the equipment and the assessments and they are used to explaining the trial to the patients. So, I don’t see an issue with those who are most involved with the study⁵⁵.

However the TC makes a valid point that with any new study even with the benefit of a pilot

“there are always going to be issues with studies in terms of the coordination of the study and the organisation of the study and making sure everybody knows what they’re doing and are well informed of what is going on and they are all trained up in the study. So, in general, I think once the planning phase is done correctly, I don’t envisage any issues with the study⁵⁵”

4.2. Resources

This section deals with assessing time and resource problems that can occur during the main study. The results in this section come from a combination of quantitative and qualitative data collection methods.

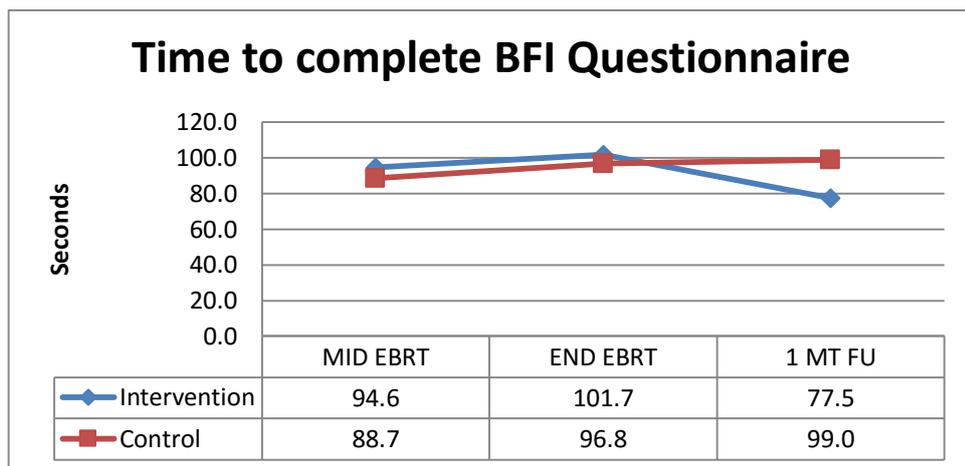
4.2.1. Key Process Times

4.2.1.1. Participant Recruitment Duration

The average time to recruit a patient at their CT appointment was 53.8 minutes (SD = 18.2)

4.2.1.2. BFI and FACT-P Completion Time

The average time to complete the BFI questionnaire was 93 seconds (SD 60.2, Range 30-351) and FACT-P 367.9 seconds (SD 205, Range 57-1315). We can see from Figure 7 below that it takes the intervention group on average longer to complete the BFI questionnaire at each assessment after recruitment. In contrast it takes them less time on average to complete the FACT-P questionnaire at each assessment (see Figure 8)



behaviour

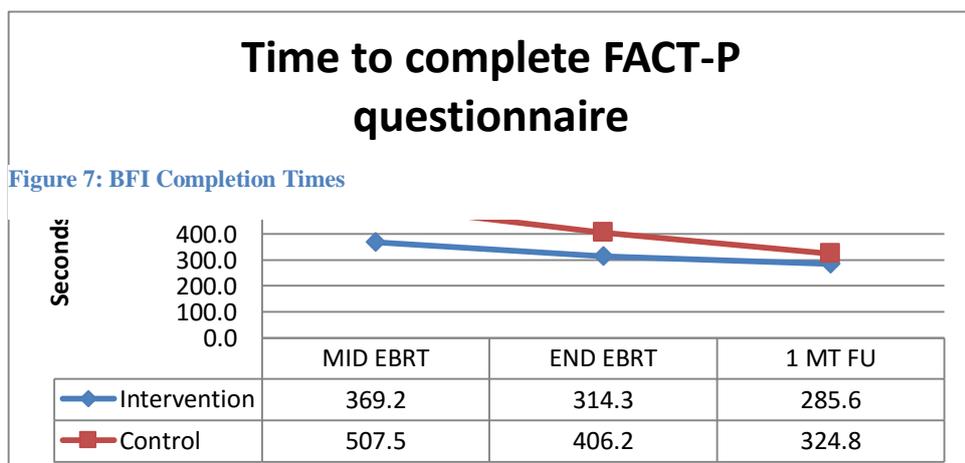


Figure 7: BFI Completion Times

Figure 8: FACT-P Completion Times

4.2.2. Room and Equipment Availability

TCs reported no issues with either room or equipment availability:

“There are two lovely little rooms beside our CT and they are not always but available the majority of the time to use. Thankfully, in this centre we are very lucky with rooms that way⁵⁶.”

“there was always a room available and the scales are very transportable so we were able to move it from room to room and the measuring tape we had anyway⁵⁷”

“Room availability worked out perfect because the clinics were running at the same time mostly so we tried to coordinate the patients with clinics. You probably could see in general with studies that sometimes, if it is a very busy clinic, it may be an issue trying to get a room so a patient may be waiting a bit longer but, as it turns out, they are probably waiting to see a doctor anyway so you can fit them in⁵⁵”

“because the PI had actually purchased scales especially for this and a tape measure and pedometers for all the patients, because all the actual equipment was purchased and I already have a desk and a computer and rights for computer access and things like that, that was all fine. There was nothing additional, there was nothing asked of the centre to provide⁵⁶”

4.2.3. SLRON Multi-Centre Willingness and Capacity

TCs at the three sites reported that they had no issues at their centres with respect to initiating and coordinating this pilot study.

“I think it had very little impact on the centre because everything about the study works around a normal radiotherapy pathway. It fits in. You can do it on the CT day, or whatever day. We didn't delay CT, we didn't delay treatment appointments, we didn't delay patients. Occasionally patients were asked to check in with reception to tell us when they were here, reception were very good at letting us know. We didn't delay follow-ups or anything like that. So the centre, I think, didn't have much hassle because they basically just transferred the patient to us and then the workload was just done by the coordinators. There is a lot of work for the coordinator from certainly the initial appointments but I don't think the centre felt the impact of that. But that would be standard for any clinical trial⁵⁶”

At one of the centres a TC raised the issues of staffing a future confirmatory future trial:

“I would say that you could have a greater rate of recruitment but you'd still have to look into issues of staffing. Staffing is always going to be an issue no matter what study you are doing. At

the moment we are probably not fully staffed but if you were to roll out a bigger study, of course, staffing would have to be adequate for you to recruit adequate numbers....,⁵⁵

4.2.4. Potential Future Resource Issues for a Future Confirmatory RCT

While TCs agreed that there were no capacity issues for the pilot study they are concerned that at current staffing levels we would not be able to continue at the current rate of recruitment.

“the only thing would be if you were to go forward with it, two patients a week amounts to quite a number of patients on review at any one time so you would probably need some extra staff. In a small pilot setting it’s not too bad but on-going in a larger trial you would need more staff available to do the assessments, particularly the longer assessments with the steps, they do take a little bit of time. You wouldn’t be able to do two or three too quickly⁵⁷”

This point is further reinforced by the other TCs:

“I think the main thing is staffing and just making sure as well, obviously, that your consultants or medical teams who are involved in the study are all on board with you⁵⁵” and

“We definitely do not have the capacity to recruit all the eligible patients. Well, in saying that, in general the centre runs about four or five clinical trials with one trial coordinator. So if this study is effectively 20% of your week, if you have only one dedicated day for this trial, that’s not enough for the number of eligible patients coming through because you do need a good bit of time for those initial assessments and follow-up assessments. It is easy to get patients on the trial but once the mid-radiotherapy assessments and post-radiotherapy assessments start clashing with new patients coming on the study that is when it gets really busy so you would need either another coordinator or fewer studies. I think you would easily have two and a half days a week worth of work with this study for one person, if you were to go for every person and it was long-term⁵⁶”

The TC goes on to explain exactly where the capacity issue would arise:

“it’s not the initial assessment that is such a big deal but doing the initial assessments and then four weeks later doing the mid-radiotherapy assessments and eight weeks later you would have patients doing all three types of assessment. It’s when you have all three; you actually have six appointments on that day. Six appointments on one day is a lot, you wouldn’t want to be doing more than six patients in one day⁵⁶”

4.3. Management

This section of the pilot study explores potential human and data management problems that could adversely affect a future RCT. All data in this section comes from in-depth interviews with each trial co-ordinator.

4.3.1. Pilot Study Management Issues

All three trial Co-Ordinators (TCs) reported that they had no issues managing this feasibility study and that: *“Everything seemed to run smoothly⁵⁵”*. One TC summarised,

“I think this study is great because it does pilot the study and I think that’s really important, that’s not usually done. What usually happens is what looks great on paper doesn’t always work in practice. You just don’t know what you’re going to come up against. In reality we end up changing CRFs or retrospectively trying to grab data that we didn’t grab or collecting data that we don’t need or we’d plan things that are more inefficient than they could be. I think, if it’s going to be a long-term study or a longitudinal design, it really should be piloted and I think it’s something that should be done more”⁵⁶

4.3.2. Data Entry Issues

TCs found data entry for the trial non-problematic overall. The only issue to emerge concerns the process of calculating intervention patients’ step targets

“There was a spread sheet that was to calculate the step targets and I found that really complicated even though I shouldn’t have. There was a calculation that you could do out manually and that would have been fine but then there was a spread sheet as well that calculated it. You put in a couple of different numbers from the pedometer but I copied and pasted them and actually deleted some of the formulae from the spread sheet which was a bit of a risk if you were collecting data in the future. To just try and test it on a few dummy run patients, either dummy run the Excel spread sheet or do a pilot study, or lock it, if there was some way of locking the spread sheet, or do them manually, I don’t know. But just to be aware that that is something that someone could mess up”⁵⁶

4.3.3. Potential New Data Values

TCs main concern was that we need to capture if and how intervention participants weight loss impacts on their EBRT treatment and dosimetric distribution in any future study. One TC commented:

“The only thing would be if you were to capture maybe whether weight loss required any of the patients to have their treatment re-planned. If they lost a significant amount of weight, it may result in a change in the patient’s contour and subsequently a change in their dosimetric distribution of their treatment. Obviously, you would like to avoid that because it is more workload on the department and it also involves more radiation dose to the patient as they are having extra scans. So, it is not an ideal situation. I: Roughly, what kind of a contour change in the patient? In excess of 1cm in any one direction”⁵⁷.

Another TC further added to this point while commenting how Radiation Therapists were not fully aware that a patient was on an exercise trial initially:

“The girls in the units were amazed by the visible [weight loss], although they actually didn’t realise that was what it was from because they weren’t totally in tune with the study in this particular case but they couldn’t understand why the patient’s contour had changed so dramatically. Eventually I mentioned, ‘actually, they are on the study, the exercise intervention, they’re walking, they’re trying to keep healthy, get healthy.’ So there was a very dramatic, noticeable increase not just in our own weekly assessments but other staff around the department noticed the improved health and fitness of the patients. That was great and something to be aware of, that it might work more than you would expect. I: Because weight loss is not always a good thing for a radiotherapy patient. That’s it, in terms of consistency and planning. From a radiotherapy perspective, it might be too good. It might not seem like they are being asked to do a lot but people who are so sedentary to begin with, it’s ideal. They can manage it but it definitely works”⁵⁶

One TC also thought that it would be useful to record physiological and biochemical tests to the study’s outcomes.

“I think it would have been great or in future it would be really interesting to look at a patient’s blood pressure and maybe their liver function tests because we could definitely see the physical impact but it would be lovely to know did we actually improve heart health in these patients”⁵⁶

4.3.4. Potential Future Management Issues for a Future Confirmatory RCT

TCs expressed no obvious management concerns. The consensus was that:

“it was a very well-coordinated trial, very easy to do.”⁵⁷ Another co-ordinator commented that “we are well used to doing studies.., and think it follows, really, the manner in which many of our studies would follow. It doesn’t stand out as being different in terms of how it would run or how we would actually go about setting up the study”⁵⁵.

4.4. Scientific

This section deals with the assessment of the interventions safety, adherence and effect on outcomes of interest.

4.4.1. Intervention Safety

There were no trial related serious adverse effects recorded. One patient in each of the intervention and control groups developed urinary issues that indicated catheterisation. Patient #4 (intervention) underwent a procedure to have a suprapubic catheter during week four of the intervention and thus could not continue with his exercise prescription. He was still followed up at the appropriate times. Patient #17 (control) had a urethral catheter inserted. This did not affect his ability to continue as a trial participant.

4.4.1.1. Treatment Toxicities

The following table (table 13) demonstrates the change in adverse events (AE) from baseline assessment to highest recorded toxicity grade throughout the intervention. For example, there was a 25% increase in grade 1 diarrhoea from baseline assessment in the intervention group compared with 16.7% in the control group.

Toxicity Grade	Intervention			Control		
	1	2	3	1	2	3
	% change			% change		
Urinary Incontinence	0	0	8.3	0	0	8.4
Urinary Frequency/Urgency	16.7	0	8.3	16.7	8.4	8.2
Dysuria	25	0	8.3	50	0	8.3
Haematuria	0	0	8.3	8.3	0	8.3
Urinary Retention	25	0	8.3	25	0	8.4
Diarrhoea	25	0	0	16.7	0	0
Proctitis	25	0	0	0	0	0
Rectal Bleeding	8.3	0	0	0	0	0
Constipation	8.3	0	0	8.3	-25	0

Erectile Impotence	0	8.7	0	0	0	0
Libido	0	0	0	0	0	0
Hot Flashes	8.4	0	0	0	0	0
Gynecomastia	0	16.7	0	0	0	0

Intervention patients demonstrated higher rates of grade 1 diarrhoea, proctitis, rectal bleeding and hot flushes, and grade 2, erectile impotence and gynecomastia (in red) than the control group. However intervention patients demonstrated lower rates of grade 1, dysuria and haematuria and grade 2, urinary frequency/urgency (in blue) than the control group. Both groups were comparable on all other measures AE's

Table 13: Intervention VS Control Participants change in adverse events from baseline assessment to highest recorded toxicity grade throughout the intervention

4.4.2. Intervention Adherence/Contamination Rates

Calculating Exercise Prescription Adherence/Contamination

A. Adherent Weeks (AW)

Exercise prescription was prescribed according to Frequency, Intensity, Time and Type (FITT) and it is best practice is to measure adherence using the same criteria³⁷. For a participant to achieve an AW they must fulfil the following criteria:

- Frequency (F); $\geq 66\%$ of prescribed exercise sessions.
- Intensity (I); $\geq 66\%$ of prescribed step/week target i.e. baseline steps + ($\geq 66\%$ of 15000) steps
- Time (T); $\geq 66\%$ of prescribed time i.e. $\geq 66\%$ of 150 minutes = at least 100 minutes
- Type (T): Walking.

B. Exercise Adherent (EA) $\longrightarrow \geq$ Individual Adherence Rate (IAR) of 66%

C. Individual Adherence Rate (IAR) $= \frac{\text{Adherent Weeks (AW)}}{\# \text{ prescribed Ex Weeks}} = \frac{x}{y}\%$

Similarly, exercise non-adherence or contamination in the control group was calculated by analysing their steps/week. If a control group participant achieved their baseline steps + ($\geq 66\%$ of 15000 steps in any week they will deemed non-adherent or an exercise contaminant. Individual contamination rates in the control group were calculated using the same logic as adherence rates in the intervention group.

There was an overall exercise adherence was 81.8% in the intervention group and exercise contamination was high at 33.3% in the control group.

4.4.3. Steps/Day Trends

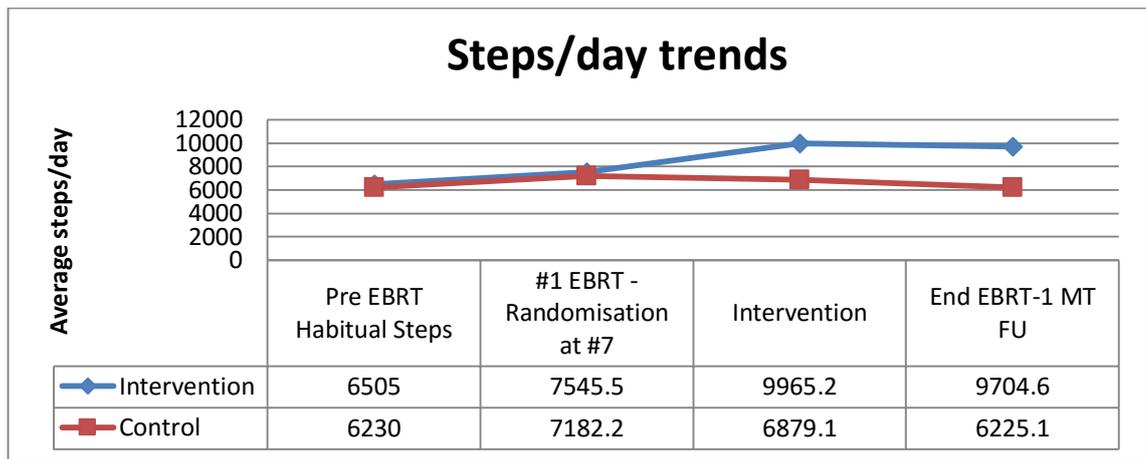


Figure 9: Group Steps/Day Trends from Baseline to 1 Month Follow-Up

Figure 9 above demonstrates that both intervention and control patients had similar average habitual steps/day before beginning EBRT (previous 7 days), 6505 and 6230 respectively. Both groups increased their average daily steps from commencing EBRT to randomisation at on average # 7. The intervention group increased their average daily steps by 16% while the control group increased their average daily steps by 15.8%.

After randomisation, the intervention group increased their average daily steps 3460 (53%) steps and the controls increased their average daily steps 649 steps (10%) compared to average habitual steps/day.

The intervention group maintained their increased average steps/day from completion of the intervention to 1 month FU, intervention participants only decreased their average steps/day by -2.6%. Control participants decreased their average daily steps by 9.5%.

4.4.4. Fatigue

Table 14 outlines Mean and SD of Overall Fatigue Scores of Both Groups from CT i.e. “Baseline” to 1 Month Follow-Up. Figure 10 demonstrates both groups mean fatigue scores of each assessment.

4.4.4.1. Overall Fatigue

	Intervention		Control	
	Mean	SD	Mean	SD
CT “Baseline”	22.2	17.6	13.4	10.7
Mid EBRT	10.9	17.7	13.4	13.4
End EBRT	7.4	11.9	15.5	13.7
1 MT FU	2.0	4.1	19.2	20.0

Table 14: Mean and SD of Overall Fatigue Scores of Both Groups from Baseline to 1 Month Follow-Up

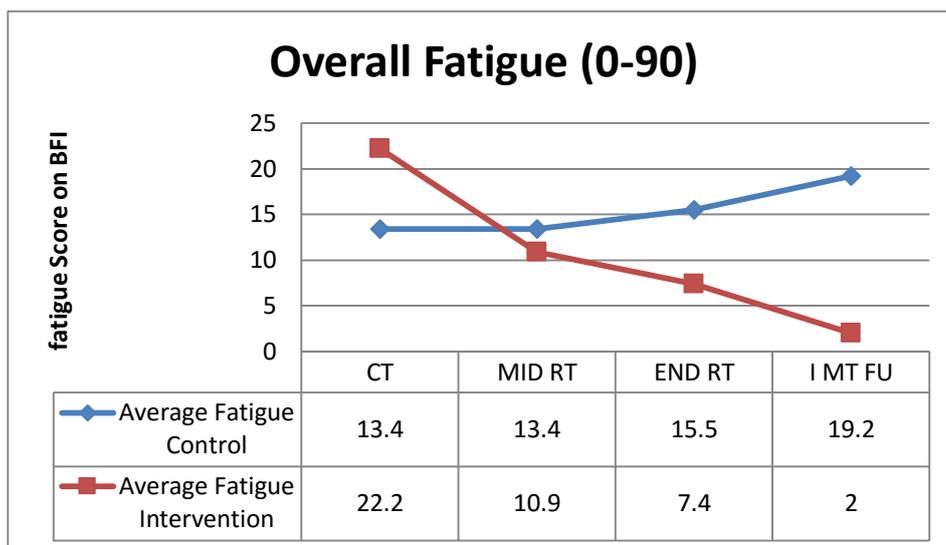


Figure 10: Mean Overall Fatigue Scores of both Groups from Baseline to 1 Month Follow-Up

We intended to calculate sample size estimates for the main study based on combinations of (i) differences in BFI fatigue scores ranging from a minimum clinically important difference of 1 to a difference of 2 and (ii) variability estimates of 2.2 to 2.8. Sample size estimates based on 80% statistical power to detect these differences between control and treatment groups using a two-tail two-sample t-test using a 5% significance level are presented in Table 10 (chapter 3). However we underestimated the magnitude of the intervention effect.

The data in table 10 (chapter 3) suggested that the numbers required to detect a minimum clinically important difference of 1 with a standard deviation of 2.6 or greater are impractical. For the main study evaluable patients are defined as those for whom BFI at one month post RT is documented, as the primary endpoint is to show that fatigue as measured on the BFI scale is less at this time point in the intervention group.

In the process of determining a sample size for the future larger study, we discovered that our pilot study was adequately powered to determine if there was statistically significant difference between groups.

The mean fatigue score difference from CT/baseline to 1 month follow-up in the intervention group was (M = -20.17, SD =15.86) and (M = 5.75, SD = 15.30) in the control group (Table 14). These means and standard deviations give an anticipated effect size (Cohen's d) of 1.67. At a desired statistical power level: 0.80 and probability level less than or equal to 0.05, a total of 14 patients is sufficient. The probability is 82 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 26 units. This is based on the assumption that the standard deviation of the response variable is 15.5. A similar one-tailed hypothesis predicts that 12 patients would be sufficient.

The dependent variable; fatigue score difference from baseline to 1-month follow-up was assessed for normality using descriptive statistics (skewness, kurtosis and distribution shape) and deemed normally distributed. The Shapiro-Wilk statistic result was also > 0.1 , this non-significant result also indicates normality.

An independent samples t-test was conducted to compare the differences in fatigue scores from baseline to 1 month follow up in the intervention and control group.

There was a significant difference in scores for intervention participants ($M = -20.17$, $SD = 15.86$) and control participants ($M = 5.75$, $SD = 15.30$; $t(22) = -4.07$, $p = .001$ (two tailed). The magnitude of the differences in the means (Mean difference = -25.92 , 95% CI: -39.11 to -12.72) was very large ($\eta^2 = 0.43$)

Additionally because of the small sample size a Mann-Whitney test was also performed. This test also gave a statistically significant result ($p < .0005$)

4.4.4.2. Fatigue Interference with 6 BFI QoL Domains

Table 15 (below) outlines fatigue interference with each of the BFI questionnaire's 6 QoL domains. A higher score indicates greater interference. Fatigue interference with each QoL domain is discussed in detail after the table.

	Baseline (CT)		Mid-EBRT		End-EBRT		1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
General Activity								
<i>Control</i>	0.5	1.2	0.5	1.4	1.1	1.7	2.0	2.9
<i>Intervention</i>	2.3	2.8	1.2	2.4	0.6	2.0	0.1	0.3
Mood								
<i>Control</i>	1.8	2.1	0.8	1.6	0.6	1.4	1.2	1.9
<i>Intervention</i>	1.9	2.4	1.6	3.5	0.7	1.8	0	0
Walking Ability								
<i>Control</i>	0.8	1.8	1.6	2.4	1.9	3.0	1.1	2.7
<i>Intervention</i>	2.4	2.8	0.7	2.3	0.4	1.2	0.2	0.6
Normal Work, daily chores								
<i>Control</i>	0.8	1.3	0.8	1.6	1.2	2.0	1.8	2.8
<i>Intervention</i>	1.8	2.3	1.3	2.7	0.1	0.3	0.2	0.6
Relations with others								
<i>Control</i>	1.1	2.1	1.1	2.1	0.6	1.0	1.1	2.2
<i>Intervention</i>	1.3	1.9	1.1	2.6	0.5	1.7	0	0
Enjoyment of Life								

<i>Control</i>	0.8	1.2	0.6	1.7	1.2	2.4	1.3	2.6
<i>Intervention</i>	1.9	2.5	0.3	1.2	0.4	1.4	0.1	0.3

a. Fatigue interference with General Activity

At CT/Baseline fatigue interfered with intervention participants' general activity more than control group participants. However it can be seen from Figure 11 that upon commencement of the exercise intervention fatigue began to interfere less with interventions participants' general activity. The opposite is true in the control group where fatigue gradually interferes more and more with control group participants.

b. Fatigue interference with Mood

Fatigue interferes with both groups' mood less and less as they progress through EBRT. However upon completion of EBRT it can be seen that fatigue continues to decrease its interference with intervention patients whereas it increases its interference in the control group as demonstrated in Figure 12.

Table 15: Between Group Fatigue Interference with 6 QoL Domains

c. Fatigue interference with

Walking Ability

Fatigue can be seen to decrease its interference with intervention group participants' walking ability from baseline to the end of the intervention (Figure 13). In the control group, fatigue increases its interference from baseline to the end of EBRT. From the end of EBRT to the 1 month follow-up fatigue can be seen to decrease its interference with walking ability.

d. Fatigue interference with Normal Work/Chores

Fatigue interferes less with intervention patients' normal work/chores as they progress through EBRT. This decrease coincides with starting the exercise intervention. There is a slight increase in interference from the end of EBRT to 1 month follow-up (0.1- 0.2). However interference at 1 month follow-up is still 9 times less than at baseline. Fatigue interferes more with control group participants' normal work/chores as they progress through EBRT (Figure 14). This interference mirrors the accepted patient fatigue experience, i.e. patient begin to experience fatigue around the middle of EBRT which continues to increase after EBRT if not treated.

e. Fatigue interference with Relations with Others

Fatigue appears to interfere with both intervention and control groups patients' relations with others to the same effect from baseline to the end of EBRT. However after EBRT fatigue interference decreases in intervention participants and increases in control participants (Figure 15).

f. Fatigue interference with Enjoyment of Life

Fatigue's interference with intervention participants' enjoyment of life decreases to coincide with participation in the exercise intervention (Figure 16). There is a slight increase from the end of EBRT to 1 month follow-up (0.1- 0.2) which coincides with finishing the intervention. Fatigue interferes more with control group participants' enjoyment of life as they progress through EBRT. This interference mirrors the accepted patient fatigue experience, i.e. patient begin to experience fatigue around the middle of EBRT which continues to increase after EBRT if not treated.

Fatigue Interference with General Activity

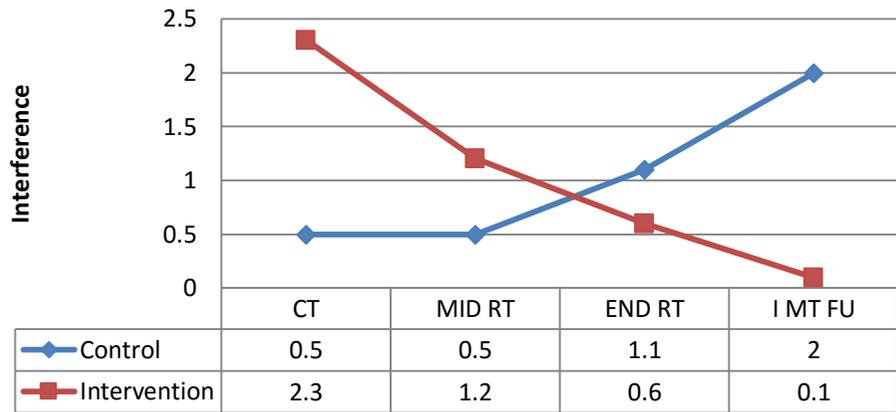


Figure 11: Between Groups Fatigue Interference with General Activity

Fatigue Interference with Mood

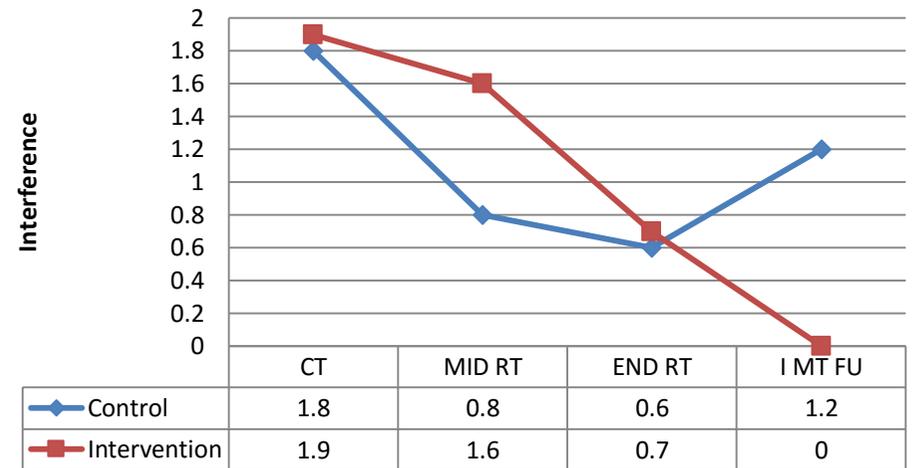


Figure 12: Between Groups Fatigue Interference with Mood

Fatigue Interference with Walking Ability

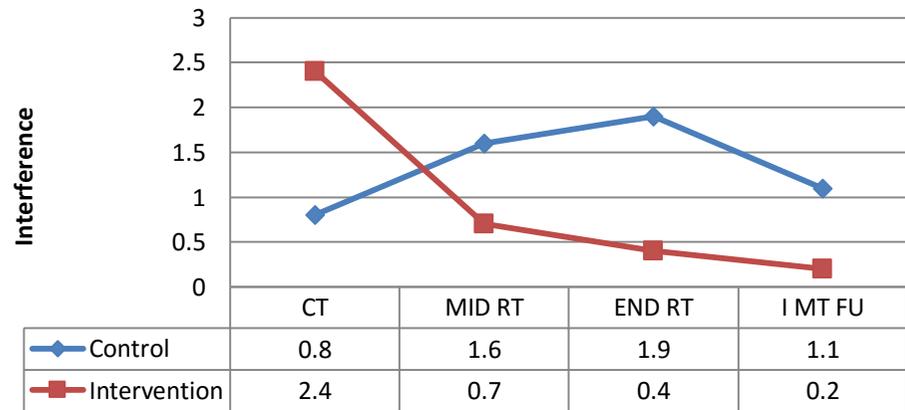


Figure 13: Between Groups Fatigue Interference with Walking Ability

Fatigue Interference with Normal Work/Chores

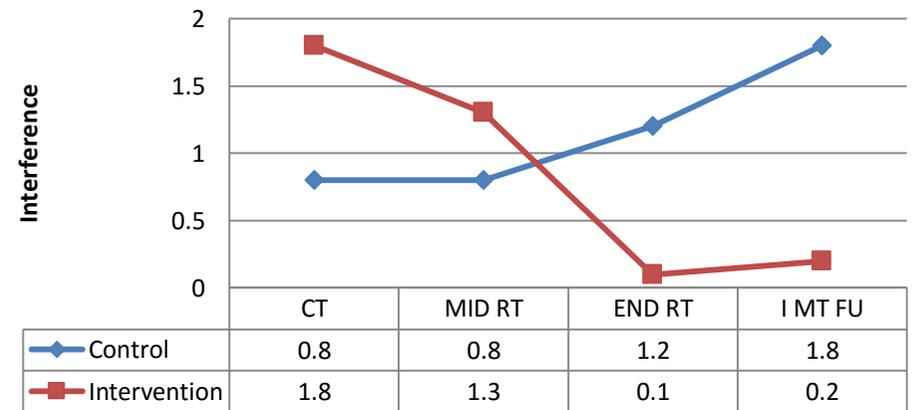


Figure 14: Between Groups Fatigue Interference with Normal Work/Chores

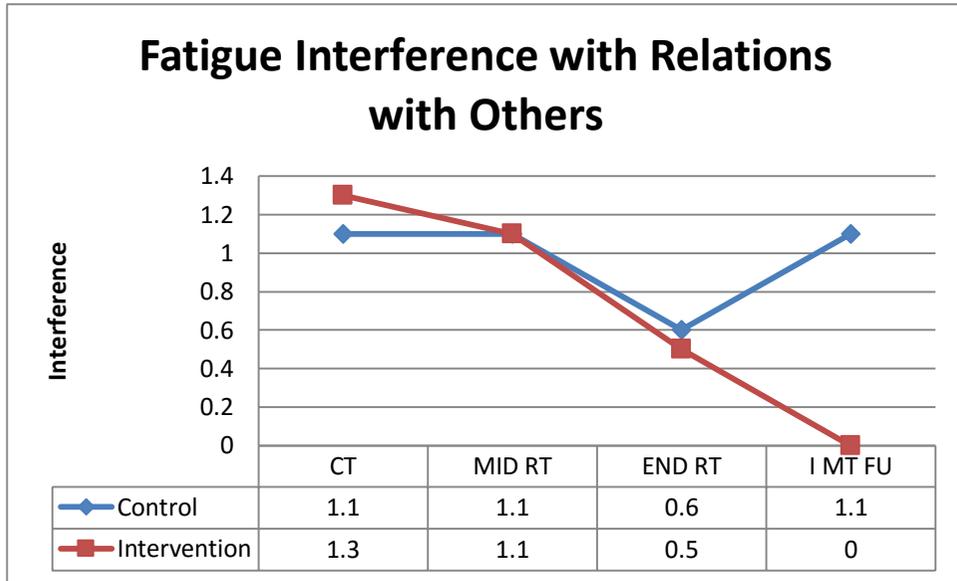


Figure 15: Between Groups Fatigue Interference with Relations with Others

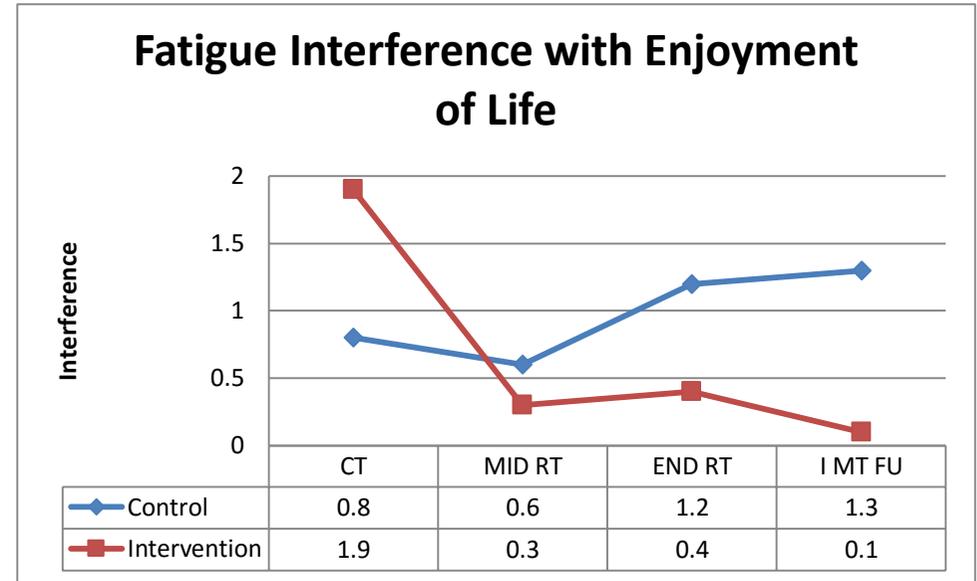


Figure 16: Between Groups Fatigue Interference with Enjoyment of Life

4.4.5. HRQOL

HRQoL was assessed at CT/Baseline, Mid EBRT, End EBRT and at 1 MT FU using the FACT-P questionnaire. The questionnaire is composed of 5 sections: Physical wellbeing (PWB), social wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing (FWB) and a prostate specific additional concerns section (PCS). The maximum score possible is 156. A higher score represents a greater HRQoL. Three scores can be determined from this questionnaire by including or excluding any of the 5 sections, e.g.

- a) **FACT-P (Overall) Total score (0-156)**
= (PWB score) + (SWB score) + (EWB score) + (FWB score) + (PCS score)
- b) **FACT-P Trial Outcome Index (TOI) Total score (0-104)**
= (PWB score) + (FWB score) + (PCS score)
- c) **FACT-G Total score (0-108)**
= (PWB score) + (SWB score) + (EWB score) + (FWB score)

Figures 17-19 demonstrate trends in FACT-P, TOI and FACT-G scores. It is clear that both groups had similar HRQoL at baseline however the intervention group participants reported a better HRQoL from Mid-RT to 1 month follow-up across all three measures of HRQoL. These three scores are discussed in more detail below.

- a) **FACT-P (Overall) Total score (0-156)** = (PWB score) + (SWB score) + (EWB score) + (FWB score) + (PCS score)

Table 16 outline how exercise intervention participants HRQoL increased from M = 126.7 (SD 19) at baseline to M = 135.8 (SD= 17.6) at 1MT FU. Control groups participants HRQoL remained almost the same over the same time period. M= 126 (SD= 15.5) to M= 129.1 (SD=20.7). Figure 17 graphically demonstrate between groups FACT-P Total Score over the 4 assessments.

FACT-P (Overall)	Baseline (CT)		Mid EBRT		End EBRT		1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Intervention	126.7	19.0	133.3	15.3	130.6	20.8	135.8	17.6
Control	126	15.5	129.5	22.7	128.6	19.1	129.1	20.7

(PWB score) + (SWB score) + (EWB score) + (FWB score) + (PCS score) = FACT-P Total score

Table 16: Mean and SD of FACT-P Overall Scores of Both Groups from Baseline to 1 Month Follow-Up

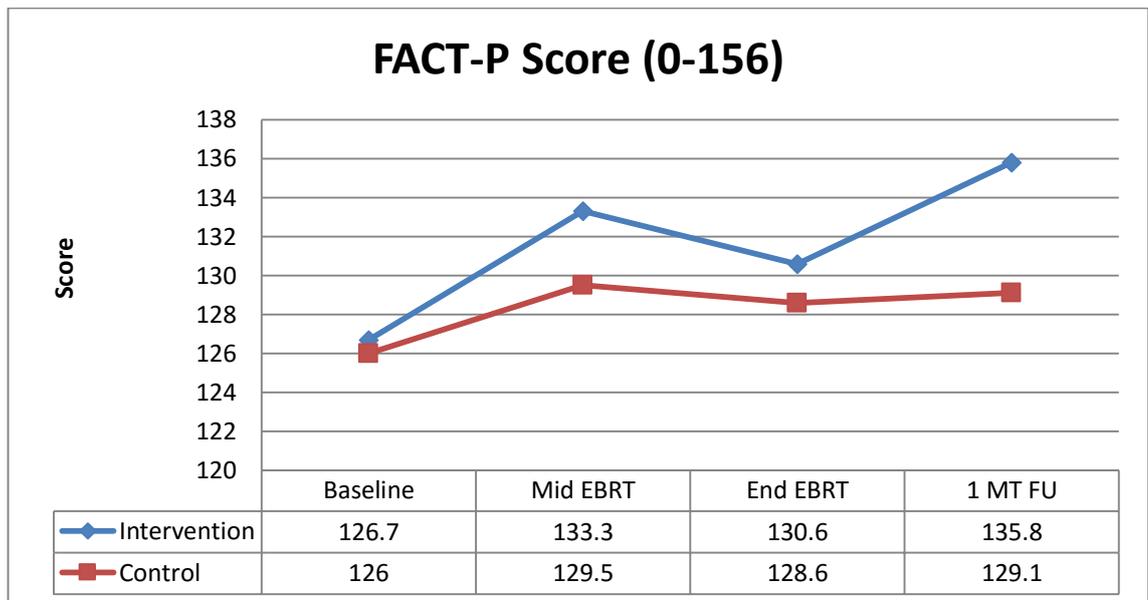


Figure 17: Between groups FACT-P Total Score

b) **FACT-P Trial Outcome Index (TOI) Total score (0-104) = (PWB score) + (FWB score) + (PCS score)**

Exercise intervention participants FACT-P TOI increased from M = 84.6 (SD 11.2) at baseline to M = 89.2 (SD= 11.8) at 1MT FU. Control groups participants HRQoL remained almost the same over the same time period. M= 82.9 (SD= 13) to M= 83.8 (SD=15.8) (Table 17). Figure 18 graphically demonstrates between groups FACT-P Trial Outcome Index Score over the 4 assessments.

TOI	Baseline (CT)		Mid EBRT		End EBRT		1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Intervention	84.6	11.2	87.7	10.3	85.7	11.8	89.2	11.8
Control	82.9	13	82.4	17.1	83.2	14.8	83.8	15.8

(PWB score) + (FWB score) + (PCS score) = FACT-P TOI Total score

Table 17: Mean and SD of FACT-P TOI Scores of both groups from Baseline to 1 month follow-up

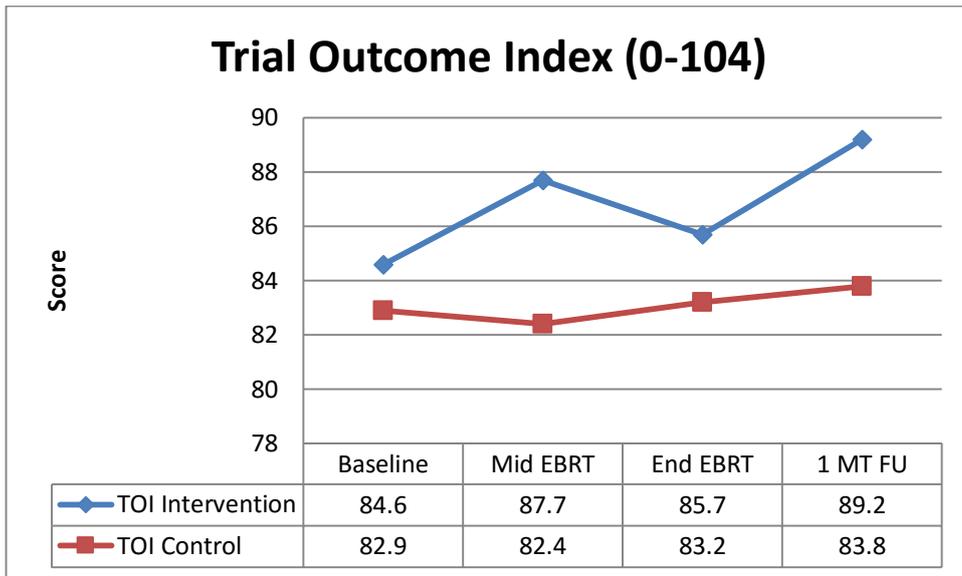


Figure 18: Between Groups FACT-P Trial Outcome Index Score

c) **FACT-G Total score (0-108)** = (PWB score) + (SWB score) + (EWB score) + (FWB score)

Exercise intervention participants FACT-G increased marginally from M = 94 (SD 17.1) at baseline to M = 97.3 (SD= 12.7) at 1MT FU. Control groups participants HRQoL increased by a similar amount over the same time period. M= 89.7 (SD= 12.3) to M= 92.8 (SD=14.1) (Table 18). Figure 19 graphically demonstrates between groups FACT-G Score over the 4 assessments.

FACT-G	Baseline (CT)		Mid EBRT		End EBRT		1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Intervention	94.0	17.1	96.0	10.4	94.0	17.1	97.3	12.7
Control	89.7	12.3	95.4	17.3	92.6	12.6	92.8	14.1

(PWB score) + (SWB score) + (EWB score) + (FWB score) = FACT-G Total score

Table 18: Mean and SD of FACT-G scores of both groups from Baseline to 1 month follow-up

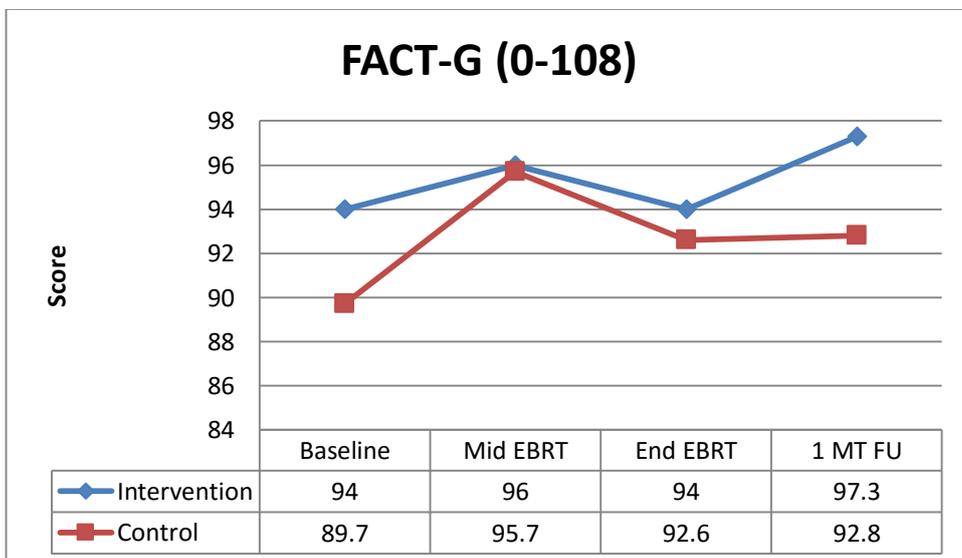


Figure 19: Between Groups FACT-G Score

4.4.6. Anthropometric Measures

Table 19 outlines changes in control and intervention groups' anthropometric measures across Baseline, Mid EBRT, End EBRT and 1 Mt Follow-Up.

Variables	Baseline (CT)		Mid EBRT		End EBRT		1 MT FU		CT-MID EBRT		CT-END		CT-1 MTFU		End -1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight (kg)																
Control	84.3	9.8	85.4	11.1	85.4	11.4	86.0	11.1	1.1	1.6	1.1	2.3	1.7	1.8	0.7	1.3
Intervention	82.3	18.8	81.9	18.4	81.6	18.3	80.6	17.2	-0.5	2.0	-0.9	2.2	-1.7	3.3	-0.8	1.9
% Body fat																
Control	26.6	4.1	28.4	4.5	28.1	5.6	27.7	5.4	1.8	3.3	1.4	5.9	1.1	3.8	-0.4	2.1
Intervention	28.7	6.8	28.1	6.3	28.7	6.6	27.6	6.9	-0.6	2.3	0	2.1	-1.1	2.7	-1.2	1.4
% Muscle mass																
Control	69.5	3.9	68.4	5.0	68.3	5.3	68.8	5.5	-1.1	3.9	-1.2	3.6	-0.8	3.8	0.4	1.8
Intervention	68.2	6.5	68.2	5.9	67.7	6.2	68.7	6.6	0	2.5	-0.5	2.5	0.5	3.2	1.0	1.4
Bone mass (kg)																
Control	3.1	0	3.1	0.3	3.0	0.3	3.0	0.2	0	0.1	0	0.2	0	0.1	0	0.1
Intervention	2.9	0.4	2.9	0.5	2.9	0.4	2.9	0.4	0	0.2	-0.1	0.1	0	0.1	0	0.1
Waist circumference (cm)																
Control	107.7	11.2	110.6	10.9	111.5	10.6	111.1	11	2.8	4.0	3.8	2.9	3.4	3.3	-0.4	1.4
Intervention	105.3	15.4	106.3	15.5	105.4	15.5	104.5	15.8	1.0	3.2	0.0	3.0	-0.9	2.9	-0.9	2.4

Table 19: Mean and SD Anthropometric Scores of Both Groups from Baseline to 1 Month Follow-Up

- Weight (KG):** Intervention participants lost M= 1.7 Kg (SD 3.3) from Baseline to 1 MT FU. Control participants gained M=1.7 Kg (SD= 1.8) over the same time period (Figure20)
- % Body Fat:** Intervention participants lost M= 1.1% body fat (SD 2.7) from Baseline to 1 MT FU. Control participants gained M=1.1% body fat (SD= 3.8) over the same time period (Figure21)
- % Muscle Mass:** Intervention participants gained M= 0.5% muscle mass (SD 3.2) from Baseline to 1 MT FU. Control participants lost M=0.8% muscle mass (SD= 3.8) over the same time period (Figure22)
- Bone Mass (KG):** Bone mass remained unchanged in both groups from Baseline to 1 MT FU (Figure23)
- Waist Circumference (cm):** Intervention participants lost M= 0.9cm (SD 2.9) of waist circumference from Baseline to 1 MT FU. Control participants gained M=3.4cm (SD= 3.3) over the same time period (Figure24)

Figures 20-24 below demonstrate changes in all anthropometric measures across the 4 assessments

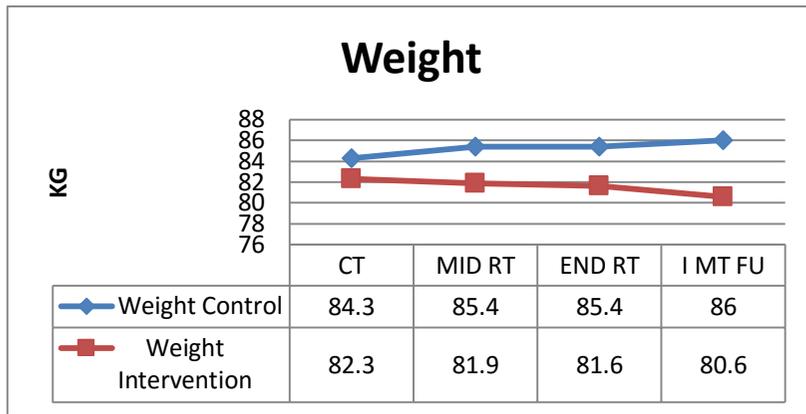


Figure 20: Mean Weight of Both Groups from Baseline to 1 Month Follow-Up

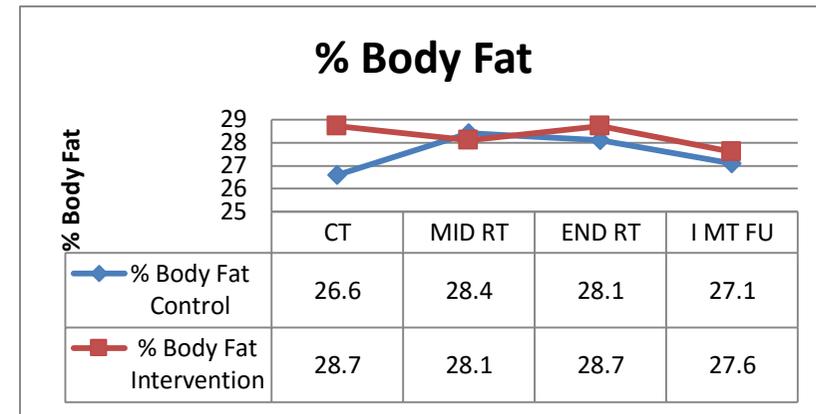


Figure 21: Mean Body Fat % of Both Groups from Baseline to 1 Month Follow-Up

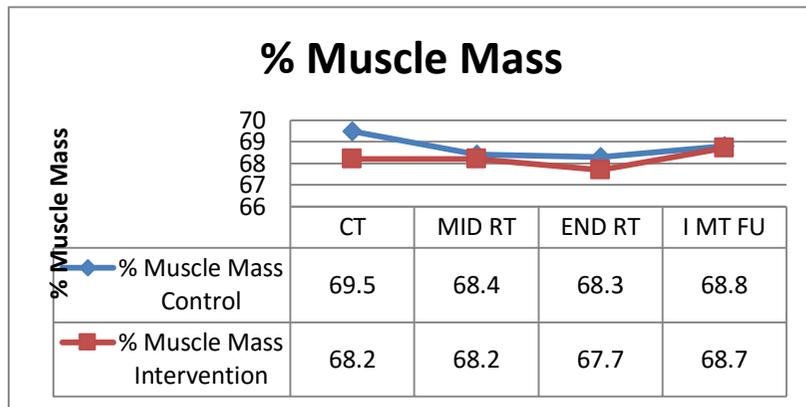


Figure 22: Mean Muscle Mass of Both Groups from Baseline to 1 Month Follow-Up

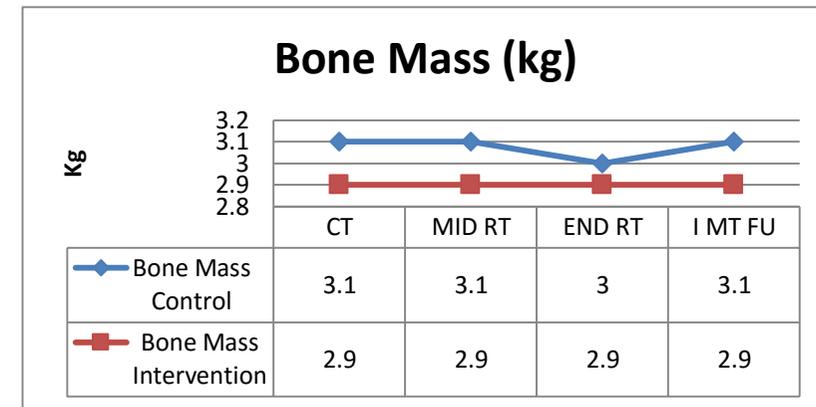


Figure 23: Mean Bone Mass of Both Groups from Baseline to 1 Month Follow-Up

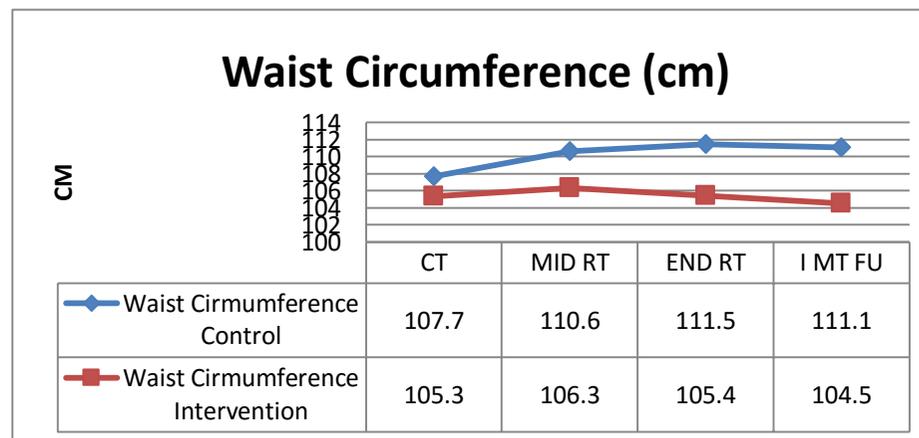


Figure 24: Mean Waist Circumference of Both Groups from Baseline to 1 Month Follow-Up

4.4.7. Physical Performance

Variables*	Baseline (CT)		Mid EBRT		End EBRT		1 MT FU		CT-MID EBRT		CT-END		CT-1 MTFU		End -1 MT FU	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2 Min Step Test																
Control	147.5	46.9	164.7	43.9	178.9	46.0	182.3	48.1	17.2	35.2	31.4	27.3	34.8	40.7	3.4	26.5
Intervention	150.8	62.8	206.1(10)	40.4	215.4 (11)	51.3	234.9 (11)	51.8	59.6	50.5	67.2	53.9	86.7	62.3	17.9	26.2
30 Sec Sit-to-Stand Test																
Control	15.4	4.3	15.7	4.8	16.3	5.5	16.8	5.3	0.3	2.1	0.8	2.9	1.3	3.0	0.5	1.6
Intervention	15.8	6.0	17.5 (11)	4.5	18.8 (11)	7.3	19.8 (11)	7.4	1.5	3.9	3.3	2.7	4.4	3.5	1.1	1.7

Table 20: Mean and SD Physical Performance Scores of Both Groups from Baseline to 1 Month Follow-Up

*All participants completed both physical performance tests except where indicated by number in brackets

- 2 Min Step Test:** Intervention participants increased their steps by M= 86.7 (SD 62.3) from Baseline to 1 MT FU. This represents an increase of 55.8%. Control participants also increased steps but by M=34.8 (SD= 40.7) over the same time period i.e. an increase of 30 %. (Figure 25)
- 30 Sec Sit-to-Stand Test:** Intervention participants increased their STS by M= 4.4 (SD 3.5) from Baseline to 1 MT FU. This represents an increase of 25.3%. Control participants also increased steps but by M=1.3 (SD= 3.0) over the same time period i.e. an increase of 9.0 %. (Figure 26)

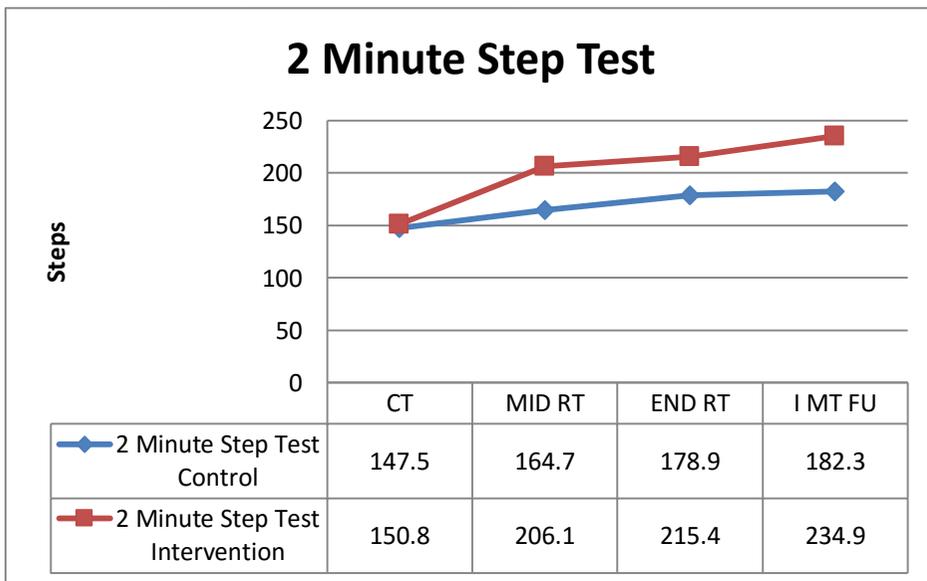


Figure 25: Mean 2 Minute Step Test Scores of both Groups from Baseline to 1 Month Follow-Up

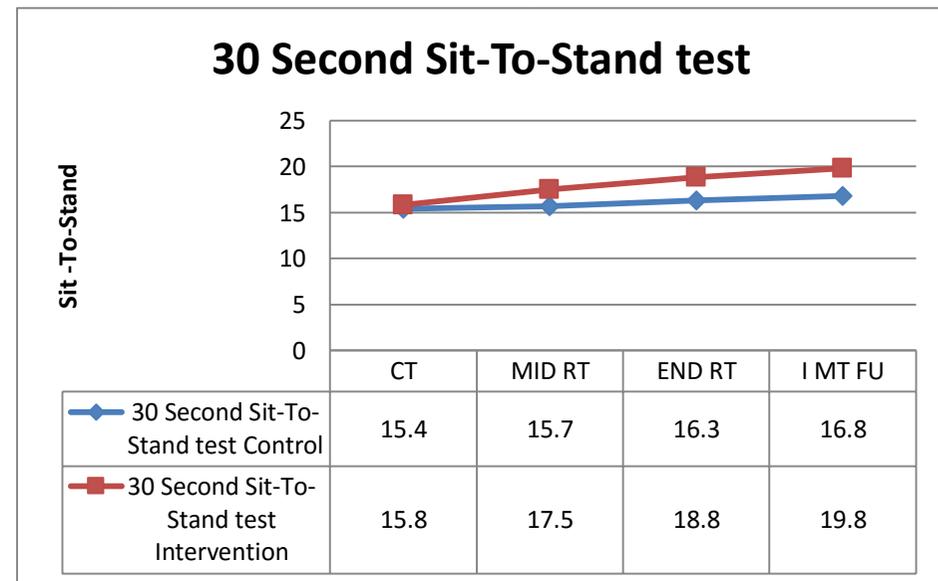


Figure 26: Mean 30 Second Sit-To-Stand Test Scores of both Groups from Baseline to 1 Month Follow-Up

4.4.8. Intervention Participants

4.4.8.1. Intervention Satisfaction

Intervention participants were invited to complete a four question survey at the end of EBRT. The questions, scales and results are displayed in table 21.

	Intervention (N=12)	
	Mean	SD
Pain or discomfort performing the walking intervention <i>(0 = No pain or discomfort, 5 = severe pain or discomfort)</i>	1.1	0.3
Programme convenience <i>(0= Not convenient, 5 = Extremely convenient)</i>	4.8	0.4
Overall level of satisfaction <i>(0 = Not satisfied, 5 = Extremely satisfied)</i>	4.8	0.4
Willingness to continue walking programme independently after intervention finishes <i>(Yes or No)</i>	100% Yes	

Table 21: Intervention Group Participants Intervention Satisfaction Scores

4.4.8.2. Intervention Barriers and Facilitators

From the literature we know that exercise interventions for patients with all types of cancer that report the highest exercise adherence rates have three intervention components in common, they: 1) set programme goals, 2) promote practise and self-monitoring, and 3) encourage participants to attempt to generalise behaviours learned in the supervised exercise environment at randomisation to other, non-supervised contexts. This intervention integrated these 3 components into its methodology. To investigate further potential exercise facilitators or barriers for PCa patients specifically, a convenience sample of 4 intervention participants were invited take part in an in-depth interview exploring barriers and facilitators to completing the intervention.

Intervention patients gave very positive feedback about their experiences participating in the intervention:

“I think the programme is of benefit to anyone because, especially with the weight, it keeps it level and it doesn’t increase during that time. It would be of benefit to your overall health and fitness⁵⁸”

“It was satisfying and I enjoyed the walking, it’s good for you and I want to keep that up⁵⁹”

“I found it satisfying... I enjoyed it. I was glad of the experience⁶⁰”

“At the beginning I found it a bit difficult, I wasn’t really used to the procedure, but then when it was explained to me that you could do it in two different sections rather than all in the one go it made life a bit easier⁶¹”

Intervention participants were generally clear of the advantages of their involvement in the exercise programme; one participant explained how it made him feel:

“Because it was benefiting myself and my own level of fitness and exercise, I didn’t regard it as an inconvenience. I accepted that it was for a purpose... I feel fitter and my mood is better that it would have been without it, in my opinion... that (intervention) was a help, to take my mind off it (cancer) and concentrate on doing the exercise and just basically forgetting about the cancer⁵⁸”

Another participant who unknown to himself at the time had increased his average weekly steps from a baseline of 43349 steps to an intervention weekly average of 73719 steps i.e. +70.1% said the following:

“Did it help me at all? I couldn’t say. I’d probably have done as much walking if I was never on the programme, I think... Or maybe I wouldn’t have done as much but I’d have tried to do as much anyway⁶¹”

No intervention participants had an overall negative experience on the trial. One participant did find the recruitment process “upsetting”:

“Well I’ll tell you what upset me in the beginning, do you remember the day when I was here for my first scan (recruitment)?.. I was to meet you as well. So, I wasn’t up to date with this water drinking and I got no information on that until my CT scan was over but what I found annoying, although I didn’t relate it at the time, what I found later was because you came on in the meantime and dragged me over to the far side of the hospital and I was up here, wherever, getting the CT scan and I was after drinking three mugs of water and then I was swept off over there, ‘C’mon over there, you’ve one in your hand there, you have to drink six more,’ you said to me. And I was thinking, if I’d been left alone without being dragged over there and back, you know what I mean. I’m not saying you, you were probably busy. If I could’ve just concentrated on the CT scan first and then go and do the other business... Get one thing out of the way first and then go and do the other thing⁶¹”

Intervention participants had generally positive feedback regarding the pedometer and logbook:

“At first I was a bit frightened I would lose it “pedometer”! But I got used to it, I used it every day, I got used to it and it wasn’t a problem... It did motivate me a bit. I exercise regularly but it was interesting to have a look at it⁶⁰”, “Yes, it was (easy to use)⁵⁸” and “no bother⁶¹”. The logbook also received positive reviews: “I just got used to it⁶⁰” and it was “Very clear⁵⁹”

Intervention participants gave very informative answers about the exercise barriers they faced throughout the intervention:

“There would be a few days that you wouldn’t feel like doing it but I forced myself to do it, I was glad afterwards⁵⁸”

“R: you might want to get it out of the way and you might be rushing, you might only get in in time to drink your water and stuff. I: And that’s because you decided to do your walking before treatment. R: Before treatment, yes. I: Do you think if you had to do it again you’d do your

walking after treatment? R: No, I'd do it the same way. I did do it after treatment sometimes. Depending on what time the treatment was at⁶¹”

“I: On the days that you didn't achieve it, which are relatively few, were there specific reasons that you couldn't do it? R: Generally, two reasons: 1) I would be travelling in a car, long journeys; and 2) weather, when it was raining. I: And on the rainy days, were they days you were getting treatment or were they weekend days? R: Generally, weekend days⁵⁹”

“The only problem was the traffic. One part has heavy traffic on the roads⁶¹”

Intervention participants also had interesting things to say about what facilitated their exercise each day:

“The programme, the study you are doing. That was the motivation⁶⁰”

“Well, because the walking in St Luke's was somewhat level, you know that was a help to me. There wasn't much hills and hollows. And also, when I went home the same would apply because I walked on the road because it was fairly flat and it was a help⁵⁸”

“Yes (the walking fitted into my treatment schedule)... It was on my mind all the time. I was trying to get the 8,000 or 9,000 every day⁵⁹”

The different environment of each hospital also had a part to play in facilitating the exercise intervention: SJH

“For me, it was very simple because I got off the train at Heuston and walked up to here. I probably would have got 15 minutes, 15-20 minutes in there. Then I walked around the grounds of the hospital outside in general and I got the 30, 35 minutes...Then I would walk at home or do something at home and get it up to the 7,000 or 8,000⁵⁹”

“Coming up on the train was handy because you could walk up from the station, that was 10 minutes or a quarter of an hour out of the way. Then you had another 15 minutes maybe around the hospital. I used to get a lift in to Portlaoise with the wife, she works in Portlaoise and some days I walk from where she works down to the station but I wouldn't include that. If I was going to do the walk, if I had time, I'd do the walk before the train, I'd walk around Portlaoise for half an hour.... Mostly, I'd come up to Dublin and walk from the station up to here... . I'd walk around the hospital and finish the half an hour before I'd have my treatment I: Were there ever days where it was raining and stuff like that? How did you handle that? R: I walked inside the hospital, yes. I: How did you find that? Was that harder? R: No, no bother, no. I: Just up and down the long corridors? R: All around the bottom, the far end over the other side near the restaurant, all down around there⁶¹”

“Most of the time from 10 o'clock in the morning and it would take me about an hour and a half to get to 9000. I walked from A to B and in near enough the half hour I would have 3000 plus steps. And then it would take another hour⁶¹”

SLH

“I chose to do the exercise in the grounds of St Luke's in Rathgar, which is a Slí na Sláinte [walk way]1km per lap. I usually did three laps of that which is 30 minutes. Sometimes I did four⁵⁸”

“It only rained say about twice while I was over there and it started during, during my 30 minute walk and I continued, continued as though it wasn’t raining. So I finished even though I got wet but that was only about two days⁵⁸”

“If my treatment is in the morning, I did it in the afternoon and if my treatment was in the morning, I did it in the afternoon⁵⁸”

4.4.9. Control Participants

4.4.9.1. Exercise Knowledge, Attitude and Practices (KAP) in the control group

Only 42% (5/12) of the control group were aware of the correct recommended weekly MVPA guidelines (Figure 27). 33% of control group participants were unaware of the adverse event reducing effect of MVPA during EBRT (Figure 28) but 92% did agree that it could improve their HRQoL (Figure 29). 58% incorrectly thought that there are genuine risks associated with MVPA during EBRT (Figure 30). 100% of the control group felt confident that they knew how to keep physically active (Figure 31) and only 50% were interested in learning more about physical activity (Figure 32).

Only 33% patients remembered a health care professional discuss the role of exercise during and after EBRT (3 Consultant, 1 Nurse) (Figure 33). 58% of patients had not changed their exercise regime from baseline to end of EBRT, 25% decreased their exercise and 17% increased their exercise (Figure 34).

Since completing EBRT 67% have not changed their exercise regime. 17% say they have decreased exercise and 17% say they have increased exercise (Figure 35).

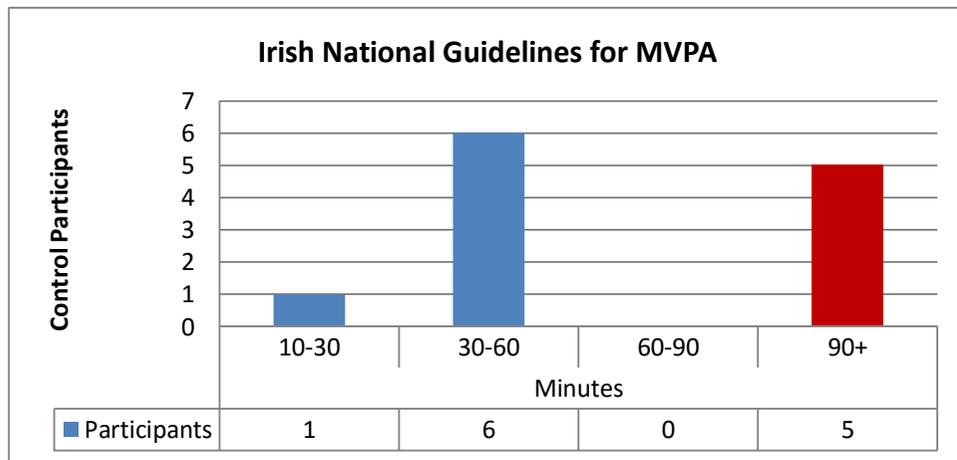


Figure 27: Control Group Participants Responses to KAP Questionnaire Q1

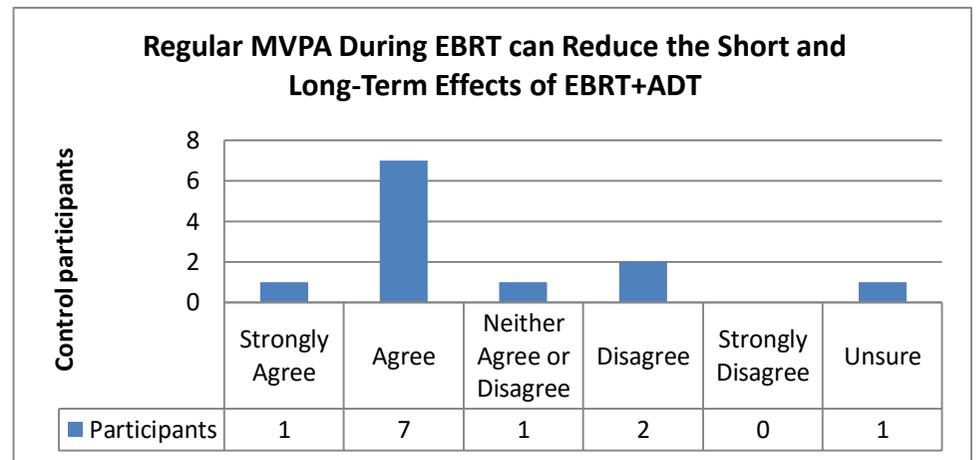


Figure 28: Control Group Participants Responses to KAP Questionnaire Q2

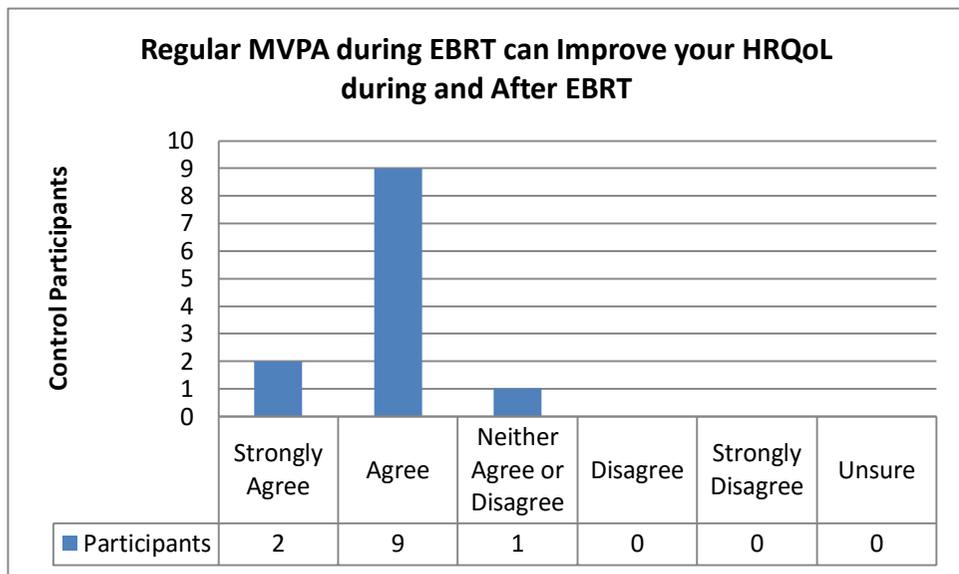


Figure 29: Control Group Participants Responses to KAP Questionnaire Q3

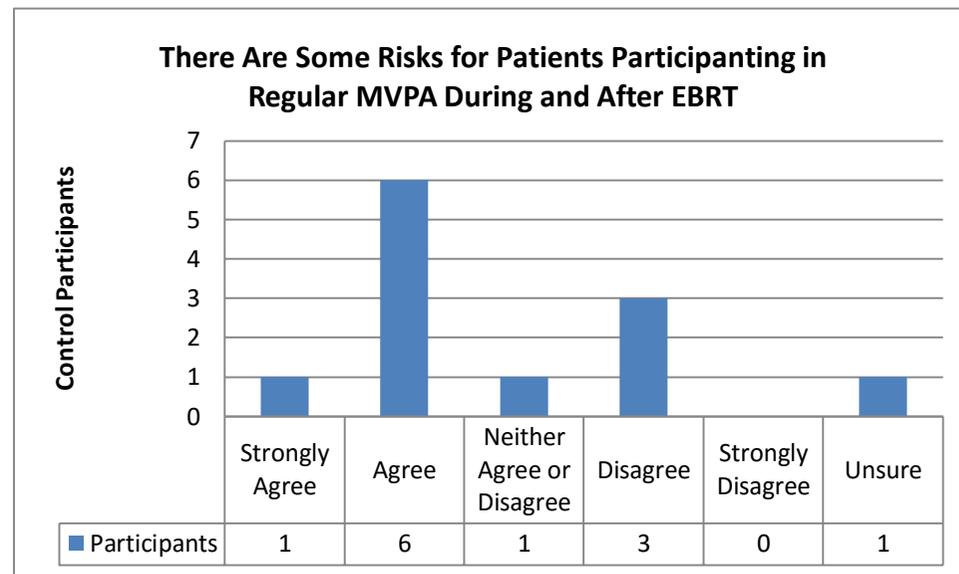


Figure 30: Control Group Participants Responses to KAP Questionnaire Q4

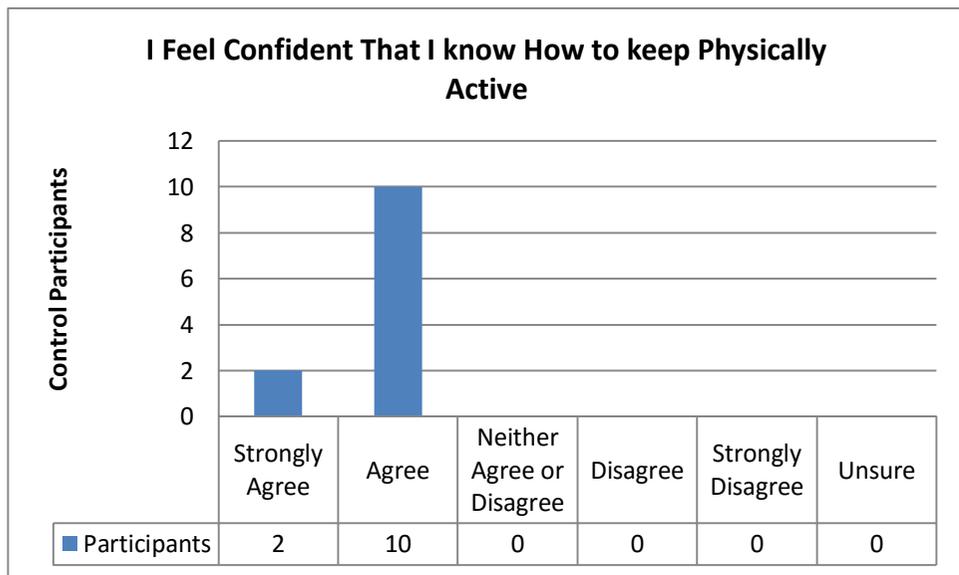


Figure 31: Control Group Participants Responses to KAP Questionnaire Q5a

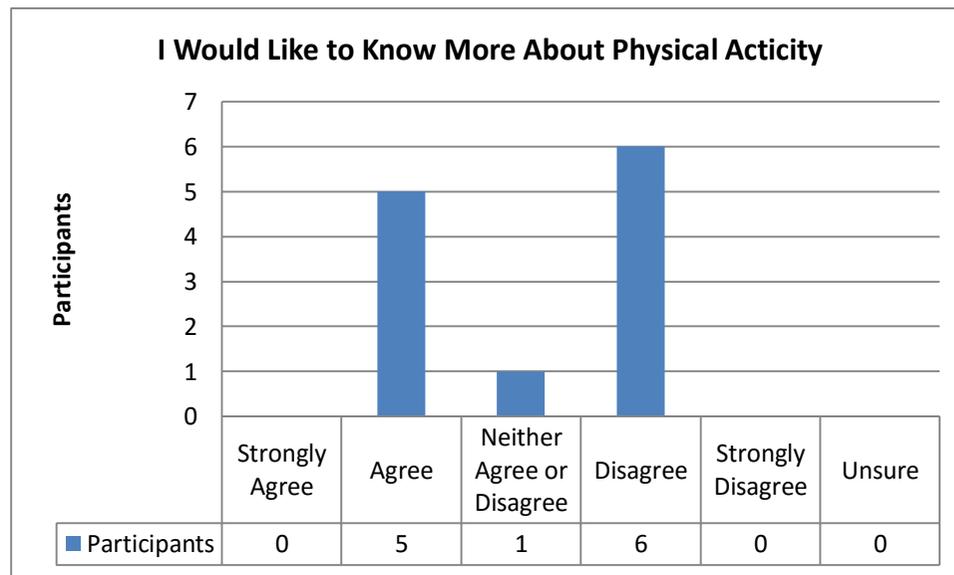


Figure 32: Control Group Participants Responses to KAP Questionnaire Q5b

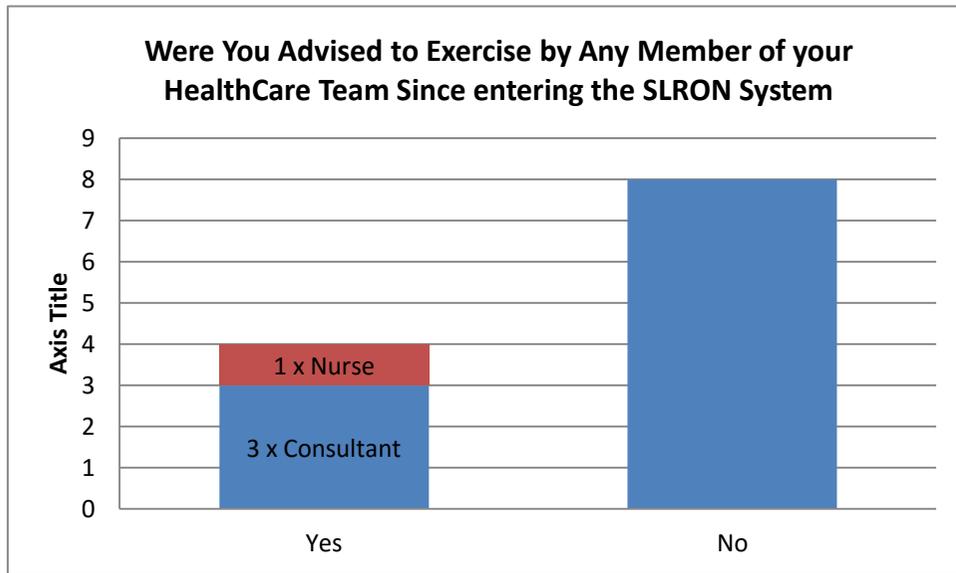


Figure 33: Control group participants' Responses to KAP questionnaire Q6a

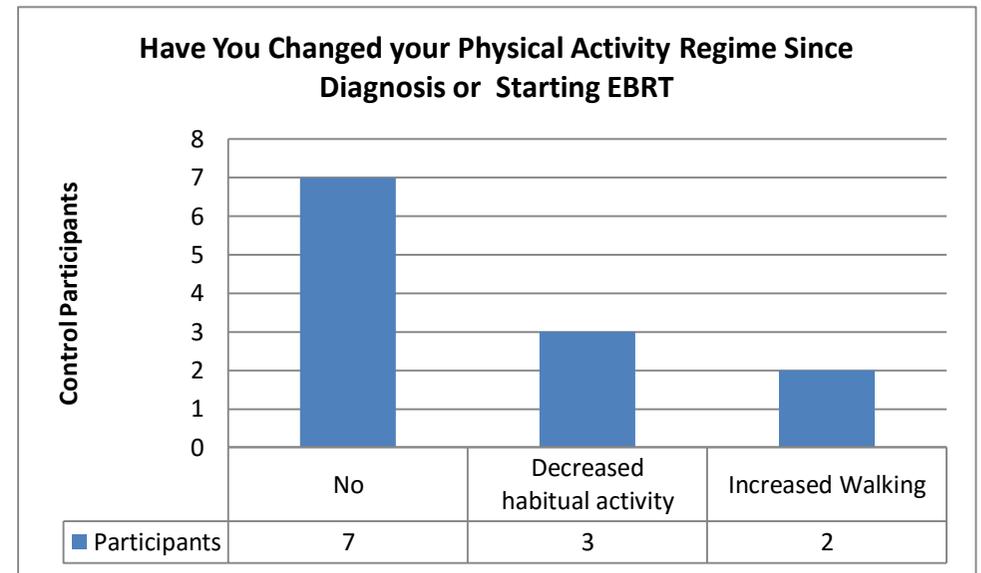


Figure 34: Control group participants' Responses to KAP questionnaire Q6b (i)

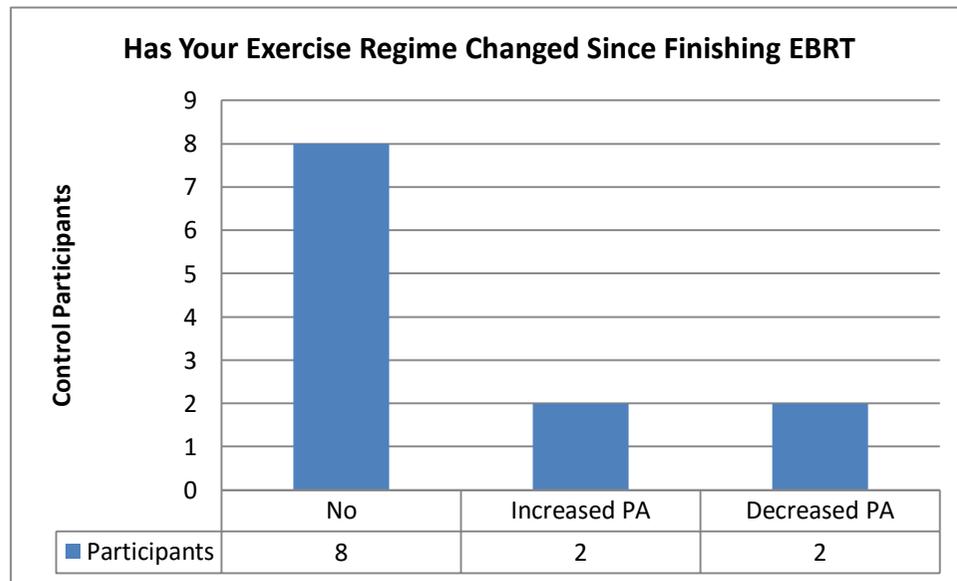


Figure 35: Control group participants' Responses to KAP questionnaire Q6b (ii)

5. DISCUSSION

This pilot study was designed to establish the feasibility of a home-based MVPA aerobic exercise intervention to reduce fatigue and increase HRQoL for patients with localised prostate cancer actively undergoing EBRT+ADT before proceeding with a future confirmatory RCT.

Similar to previous systematic reviews^{4,5,15,18}, this study further adds to the existing evidence to suggest that physical activity interventions offset many of the side effects of EBRT+ADT with few side effects itself^{4,5}.

This is the first study to demonstrate that a home based MVPA walking exercise intervention during EBRT is safe and associated with high compliance and reduced fatigue among patients undergoing radical EBRT for PCa. These findings support the hypothesis that in any proposed future confirmatory study, patients in Ireland with localised prostate cancer undergoing radical EBRT+ADT randomised to the MVPA walking exercise intervention will experience less fatigue in comparison with the standard care control group over the period of radiotherapy treatment and at 1-month follow-up.

This pilot study was planned as a preparatory study designed to test the feasibility of the processes, resources and management issues under consideration for use in a future confirmatory RCT⁶². It has comfortably satisfied the feasibility criteria for SLRON to recommend a future RCT. In advance of a discussion on the scientific outcomes of this pilot study, firstly we will discuss the process, resource and management outcomes and subsequent issues that could create obstacles to completing a future confirmatory RCT. Finally we will discuss the pilot study results in the context of the feasibility or “stop/go” criteria, and interpret whether it is feasible to proceed to the main study.

Processes

We assessed the feasibility of the steps that need to take place as part of the main study².

86% of eligible participants were recruited to the pilot intervention (**Satisfying feasibility criteria 1**). The target accrual of 24 participants was achieved in 6 weeks, well in advance of schedule (**Satisfying feasibility criteria 2**). Unfortunately no patients could be recruited in the SLH centre as network policy during this time determined that all radical PCa patients be treated at the BH and SJH centres. A greater number of patients were recruited at SJH as more PCa patients were referred there for treatment. The issue of referring patients to each centre is decided by a central booking office and is dictated by the availability of treatment slots. This system is independent of the Clinical Trials Unit.

Trial co-ordinators (TC) reported no issues understanding the trial eligibility criteria and determining patient eligibility. TCs found the criteria in keeping with the ICH-GCP guidelines and would not recommend any changes for a future confirmatory RCT.

One TC did suggest that we should consider recruiting patients earlier than at their CT scan as patients' have already begun ADT by this time. They suggested that participant recruitment should happen at the same appointment as their ADT is prescribed. While this would be a true pre-hormone baseline assessment, it would not be feasible to carry out the functional fitness or anthropometric assessments at these appointments for a number of reasons. Namely, patients are often prescribed ADT in hospitals outside the network prior to referral to SLRON. Clearly it would not be feasible recruit these particular patients as we have no staff or authority in these centres. Additionally it would be unethical to ask Radiation Oncologist or Urologists to hold off on prescribing ADT until patients attend the SLRON for the sole purpose of potential recruitment to a clinical trial.

Participant refusal to participate rate was very low at 7%. No recruited patient refused to be randomised or withdrew from the study after allocation to either the intervention or control arm. The retention rate was very high at 96% (**Satisfying feasibility criteria 3**). Only one patient could not complete his prescribed exercise prescription due to treatment related grade 3 urinary pain and retention. This adverse event resulted in the patient undergoing a procedure to insert a supra-pubic catheter. Grade 3 urinary pain and retention are both rare side effects of EBRT.

The baseline distribution of anthropometric measures, time since diagnosis, baseline steps per day, functional fitness, age, T-stage, risk group, EBRT, ADT and social characteristics (table 11) were similar in both groups. These measurements are also similar to four previous

EBRT+ADT studies. Intervention group participants were slightly more fatigued than the control group (by chance as participants were randomised) but reported a similar HRQoL as control group participants' pre-randomisation. These patient characteristics are comparable to other studies looking at the effects of exercise intervention and are representative of radical prostate cancer patients across the network.

The schedule of assessments (table 12) appears evenly distributed between groups. Participants in each group were assessed at roughly the same fraction and with roughly the same amount of days between assessments.

TCs had no issues administering the study questionnaires. Both the BFI and FACT-P are designed for either self or co-ordinator administration. When given the choice, all participants choose to have the co-ordinator administer the questionnaire. This is in keeping with other studies in the SLRON network. According to TCs there are several reasons why participants like to have the questions read to them, in particular poor eyesight and unfamiliarity with completing questionnaires. In SLRON all trial co-ordinators are experienced researchers and receive specialised training from ICORG in how to administer questionnaires in a way that will not bias participant responses. In addition co-ordinators are trained to recognise courtesy bias i.e. the tendency for respondents to give answers that they think the interviewer wants to hear, rather than what they really feel.

TCs checked log books weekly for data quality and reported that some intervention participants found the log book hard to follow at first and required further instruction, after which they had no difficulty. Other TCs reported that participants had no issues at all. In a future confirmatory study participants would benefit from more education and training in how to complete the log book.

TCs are used to operating high-tech machinery on a daily basis and thus had minimal issues operating the body composition analyser. TCs had mixed experiences with the pedometers. In the majority of cases both the coordinator and participants had no issues using them. In some cases coordinators found them difficult to program and not very user friendly. Despite receiving clear verbal and written instruction not to keep the pedometer near cell phones some participant did. Participants were constantly reminded that this could affect data storage. Fortunately there were no issues. In a future RCT both coordinators and participants would benefit from further training in pedometer use. It would also be worthwhile investigating the availability of radio frequency (RF) resistant pedometers or RF resistant cases for the existing pedometers.

TCs were very supportive of this pilot study and how it served to bring to light potential process issues for a future confirmatory RCT. They were appreciative for the opportunity to increase their familiarity with the trial processes which will increase their confidence and efficiency in the future confirmatory RCT. Indeed they suggest it would be sensible to carry out pilot studies for all future RCTs in the SLRON network.

Resources

The researcher assessed the time and resource issues that could occur as part of the main study. A key component in planning a future RCT is estimating the necessary resources. Recruiting patients to a clinical trial is time consuming and often a limiting factor in patient accrual. The average time to recruit a patient to this pilot study was 53.8 minutes (SD 18.2). This is in keeping with recruitment times to other trials in the network. TCs did not find the recruitment process unnecessarily time consuming or in need of change for the large RCT.

Completing questionnaires is often the most time consuming component of a clinical trial assessment. The sample population in this pilot opted to have a trial coordinator talk them through the questionnaires. This is common in clinical trials in the SLRON network, and highlights the necessity of questionnaires that are validated for both self and trial coordinator administration.

The average time to complete the BFI questionnaire was 1.55 minutes (SD 1) and FACT-P 6.13 minutes (SD 3.42). No other studies have reported on completion times so we cannot make a comparison. TCs felt that these are reasonable completion time for such questionnaires and not of concern for trial coordinators. Patients became progressively slower completing the BFI questionnaire as they progressed through the study. We can also see that in general intervention participants took slightly longer to complete the BFI than control participants. In contrast, patients became progressively faster completing the FACT-P questionnaire and control participants took slightly longer to complete the FACT-P than intervention participants.

Usually patients are recruited to clinical trials at out-patient visits and on-treatment trial assessments coincide with patients' daily EBRT appointment. In both instances, appointment times change regularly for a number of reasons, namely machine breakdowns or services. During such unforeseen changes to scheduled appointments, TCs need to have quick access to a room and the necessary equipment to complete the trial assessment.

As this is a multi-centre trial each centre has its own unique challenges. Fortunately, TCs reported no issues accessing clinic rooms for either recruiting patients or on-treatment

assessments. Likewise, there were no issues accessing the necessary equipment i.e. body composition analyser, tape measure and PC.

Hospitals are busy settings in which to carry out research. Research like the current pilot study requires the cooperation and willingness of a multi-disciplinary team i.e. Doctor, Nurses, Radiotherapists, and administrative staff. It is the trial coordinators responsibility to synchronise these staff to ensure patients are recruited to studies in a controlled manner. In this instance, Consultant Radiation Oncologists backed the study and enthusiastically consented patients. This willingness filtered down through the rest of the allied health professions and made coordination easier.

TCs reported that this enthusiasm developed as a result of the minimal impact that the trial had on the normal patient pathway. In-depth knowledge of how the SLRON works regarding patient referral and treatment planning pathways played a major role in the design of this study.

As with any study with a high recruitment rate, staffing is an issue. TCs were in agreement that while we had sufficient TC staff to manage 24 patients we would need more staff at each centre for a larger RCT even at the same rate of recruitment. Recruiting 2 patients a week for a 7 week study would mean you would have 14 patients at various stages after 7 weeks. This number escalates week after week. There are an insufficient number of TCs in the network to recruit patients at the current rate for a larger study. The SLRON would need to either recruit more staff or limit the rate of recruitment.

Management

The researcher assessed the potential personnel and data management issues at each of the three participating centres.

This study was designed around the SLRON's existing clinical trial systems and structure. In doing so, the researcher was able to minimise potential trial management issues. All three TCs reported that they had no major issues managing patients on this trial. One TC suggested that we should pilot all our studies in future as what "looks great on paper doesn't always work in practice"⁵⁶.

TCs had no issues with data entry except for calculating intervention participants step targets. This calculation is done using an excel spread sheet. While the process is simple, it appears that it is not user friendly. TCs suggested that either this spread sheet is simplified or TC's should receive more training on its use.

Weight loss in the intervention group was an unexpected outcome. At best we had anticipated no weight gain. While weight loss as a result of MVPA is beneficial for a patient's health, too much weight loss may become problematic from an EBRT treatment and dosimetric distribution point of view. As a patient loses weight his external contour decreases. As a consequence, the distance from the patient surface to the prostate decreases. As this distance changes from that of the planned distance, the distribution of radiation to the prostate and organs at risk also changes. Weight loss also has implications for radiotherapists trying to get the patient into the treatment position daily using external skin tattoos. A contour change of 1 cm in any direction as verified using the linear accelerator's (treatment machine) on-board imaging facility would require the patient to undergo a treatment "re-plan". This should be avoided as the patient would be subjected to more scans and thus unnecessary radiation exposure. The added workload would also be a drawback.

Intervention patients lost an average of 0.9 kg (SD 2.2) from their CT scan to the end of EBRT. Fortunately this did not translate into a contour decrease of ≤ 1 cm. In one case it was necessary for a Consultant to assess a patient's scans. The Consultant determined that it was safe to proceed. In a future trial, there would need to be a provision for this situation. For example; if the radiotherapist identifies that a patient's contour is decreasing (visually or imaging), they should immediately notify the TC. The TC should then reassess the volume of MVPA prescribed to the patient and reduce as appropriate. There are three key points to note: firstly, the principal investigator should ensure that all radiotherapists are aware that the patient is on an exercise trial, secondly; a contour change is a possibility, and finally, a system to communicate efficiently with the TC is important.

It was also suggested that we consider a translational component in any future trial. This would involve regular blood and/or urine sample collection. The samples would then be analysed in a lab to investigate how proteins or other markers of interest change with respect to exercise. Other physiological measurements could also be considered such as blood pressure.

The overall TC consensus was that this pilot study integrated seamlessly into the existing management structures of SLRON. It is not anticipated that there will be any future management issues.

Scientific

The following section contains a discussion on intervention safety and participant adherence, fatigue, HRQoL, anthropometric measures and functional fitness. We will then discuss intervention participants' acceptance of the intervention and potential issues for future intervention participants, followed by a discussion of control participants' exercise KAP.

Safety

As with any treatment, adverse effects and safety are key concerns⁶³ for exercise interventions. There were no exercise related adverse or serious adverse events reported for this pilot study **(Satisfying feasibility criteria 4)**. It would appear that the individualised step-based MVPA exercise prescription used in this study is safe and well tolerated by patients undergoing EBRT+ADT. This outcome is similar to other intervention for PCa patients undergoing ADT and EBRT+ADT.

Gardner⁶³ (2014) in his review "the effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving ADT" reported that exercise interventions were well tolerated by participants, with a low frequency of adverse events. In addition, he also reported that exercise did not seem to affect PCa progression or ADT efficacy⁶³. However the current research is more concerned with PCa patient undergoing EBRT+ADT.

One supervised and one home-based exercise intervention^{33,34} included in this pilot study's review of patients undergoing EBRT+ADT looked at exercise related adverse events. Segal *et al*³³ reported that two patients without a cardiac history experienced adverse events (syncope and acute myocardial infarction) related to supervised aerobic exercise (cycling, jogging or cross training). Only the acute myocardial infarction was deemed a serious adverse event (requiring hospitalisation or disability). Both participants made a full recovery. Truong *et al*³⁴ reported that there were no cardiovascular complications, musculoskeletal injuries, or other adverse events related to their home-based walking exercise. This study adds further to Truong *et al*³⁴ evidence that a pragmatic home-based aerobic exercise is safe and well tolerated by PCa patients undergoing EBRT+ADT.

Treatment Related Adverse Events

To the best of the author's knowledge, this is the first study to record and report radiotherapy treatment related adverse events for patients undergoing an exercise intervention. Intervention participants experienced slightly higher rates of grade 1 diarrhoea, proctitis, rectal bleeding, and hot flushes and grade 2 erectile impotence and gynecomastia. However they demonstrated lower rates of grade 1 dysuria and haematuria, and grade 2 urinary frequency/urgency. Both groups were comparable on all other measures of adverse events. There was no clinically significant

difference in adverse events experienced between groups. The rates of adverse events are comparable to the non-trial population. This evidence suggests that the MVPA exercise prescribed in this intervention does not affect the rate of treatment related adverse events experienced by PCa patients undergoing EBRT+ADT.

Intervention adherence/contamination rate

Adherence to exercise is often considered the Achilles heel of an exercise intervention³⁷ and is a key weakness in previous EBRT+ADT studies. Exercise adherence has been defined as the degree to which a person completes a given exercise prescription. Most authors of both ADT and EBRT+ADT exercise intervention do not describe the intervention's adherence criteria. In fact none of the previous four EBRT+ADT interventions controlled for adherence to "exercise intensity" the most crucial health determining component of physical activity. In addition, in most interventions it appears that adherence is recorded using patient reported subjective tools e.g. a logbook.

This study was informed by research carried out on cardiology patients³⁷ and took an abstract public health heuristic of walking for 150 min/week at a MVPA and transformed it into a real step target. We considered the total amount of exercise performed i.e. frequency, intensity (steps and time). An individualised pre-specified threshold was identified for each patient and the percentage of participants achieving that threshold was determined⁶⁴. There was an overall exercise adherence of 81.8% in the intervention group (**Satisfying feasibility criteria 5**) and exercise contamination was 33.3% in the control group.

Home-based programs are particularly subject to questions about whether participants adhere to exercise recommendations during the intervention in the absence of direct supervision. This issue is important since adherence to exercise recommendations in RCTs is critical to the validity of the outcomes⁶⁴. We employed a number of evidence based measure to encourage adherence as outlined previously in section 2.3.3

ADT

The self-reported adherence to supervised exercise for prostate patients undergoing ADT treatment ranges from 78% to 100%⁶³. Of these ADT-only interventions, only Bourke et al⁵¹ reported adherence to unsupervised exercise. As part of a supervised aerobic and resistance exercise intervention for metastatic prostate cancer patients, participants were asked to undertake at least one self-directed 30 minute independent exercise session in week 1-6 and two independent sessions in weeks 7-12 of the intervention using the skills taught in the supervised sessions. Adherence was reported as 82% however it is unclear how adherence was assessed. There are three potential explanations for such high adherence rates for these ADT only studies:

1) They are self-reported, 2) They are predominantly supervised and 3) patients are not undergoing EBRT concurrently. One would expect lower adherence to home-based exercise interventions.

EBRT+ADT

Three exercise interventions for PCa patients undergoing EBRT+ADT reported adherence to prescribed exercise. The three studies appear to have used entirely subjective methods of exercise adherence assessment. Segal *et al*³³ reported a median adherence of 85.5 % to a supervised 24 week exercise intervention of either aerobic (cycle ergometer, treadmill, or elliptical trainer beginning) or resistance exercise (leg extension, leg curl, seated chest fly, latissimus pulldown, over- head press, triceps extension, biceps curls, calf raises, low back extension, and modified curl-up). No adherence criteria are reported, however we do know that it was subjectively assessed by exercise specialists.

In the Windsor *et al*³⁵ home-based, moderate intensity intervention, intervention participants were prescribed continuous walking for 30 minutes on at least 3 days of each week of radiotherapy at a target heart rate of 60–70% calculated maximum heart rate (as a guide to the intensity of the activity). The duration of activity and the heart rate before and at completion of activity were recorded using a wrist-band heart-rate monitor. Patients in the control group were not discouraged from performing normal activities but were advised to rest and take things easy if they became fatigued.

Adherence was self-assessed. All patients kept a patient-activity diary during radiotherapy detailing the frequency and duration of the walking intervention together with the heart rate achieved (exercise group) or the frequency and duration of everyday aerobic activity (control group). The control group showed a small, non-significant decline in hours of reported aerobic activity per week during radiotherapy. All patients in the exercise group recorded at least 1.5 hours of aerobic exercise at the recommended percentage maximum heart rate per week throughout radiotherapy. The increase in hours of prescribed exercise during radiotherapy did not achieve statistical significance (Week 1 compared with Week 5: P=0.056).

Truong *et al*³⁴ asked participants to walk for at least 20 minutes/day, 3 days/week over 12 weeks at a perceived moderate intensity of 60%-70% of age-predicted heart rate, starting one week prior to commencing EBRT. They reported a study completion rate of 84%. Of the 84 participants to complete the intervention 88% met or exceeded the exercise requirements with respect to frequency, intensity and/or duration of exercise. As in Windsor's study above, adherence was self-reported using subjective tools such as a log book.

None of the three exercise interventions for PCa patients undergoing EBRT+ADT, whether supervised (Segal) or home-based (Windsor and Truong), used an objective tool to measure adherence or provided enough detail to allow comparison to the current study.

Current Research

In this pilot study, exercise was prescribed according to the F.I.T.T acronym and adherence was determined in a similar manner. We used a stricter adherence criterion than previous studies. We also utilised a pedometer as an objective tool in conjunction with the subjective logbook to measure adherence. Despite using more stringent criteria there was an overall exercise adherence of 81.8% in the intervention group and exercise contamination was 33.3% in the control group

To the best of the author's knowledge this is the first exercise study either supervised or home-based to include a step based target as an objective assessment of adherence. It is also the first study to use a pedometer as an objective measurement tool. As opposed to the heart rate monitor used by Windsor et al, the pedometer records data that can be independently verified by the researcher.

This is the first home-based walking exercise intervention using tailored step based exercise prescriptions. Using strict and objective adherence criteria based on the F.I.T.T. principles, we have demonstrated adherence rates in the intervention group that are comparable to supervised exercise programs.

This is also the first exercise study for patients undergoing EBRT+ADT, to assess exercise contamination in the control group. Truong *et al*³⁴ recognise that their lack of data on contamination in the control group is a limitation of their research. A 33% exercise contamination rate in this study demonstrates the need to assess this outcome and regularly remind control participants not to purposefully increase their volume of exercise as per the trial protocol.

Steps/day

It is evident from the literature review that there is little evidence to inform researchers about baseline/habitual steps/day for PCa patients. This is, to the best of the author's knowledge, the first study to do so. Independently recorded pedometer data demonstrated that both groups of patients had similar habitual steps/day before EBRT. Contrary to our expectations both groups of patients increased their average daily steps by a similar amount during the first week of EBRT (#1- #7). We had expected that patients' average daily steps would decrease upon commencing EBRT due to increased travel and the actual treatment process each day. This is

the first study to investigate and indeed report that EBRT patients increase their average daily steps upon commencing EBRT.

During the study, the intervention group increased their average daily steps by 3460 steps (53%) to 9965 steps per day. We can logically assume that this increase is as a result of the exercise intervention and that at least 3000 of these steps are at a moderate to vigorous intensity. On average, intervention patients exceeded their weekly step target by 15.3%. This increase in steps almost brings the intervention group in line with the internationally recognised steps/day guideline of 10000 steps per day.

Again, contrary to our expectations, control participants increased their average daily steps by 649 steps (10%) to 6879 steps per day compared to average habitual steps/day during the pilot study. We cannot make any assumption as to the intensity of these steps. It is important to note that this average is well below the internationally recognised steps/day guideline of 10000 steps per day.

It is perhaps most satisfying that at 4 weeks post intervention (1 month FU assessment) the intervention group generally maintained their increased average steps/day. Intervention participants only decreased their average steps/day by -2.61%. Control participants decreased their average daily steps by 9.5% from an already lower baseline.

Fatigue

Data has emerged in recent years advocating the superior effects of exercise over other therapies in reducing cancer related fatigue in patients with different malignancies. To date the majority of research has involved breast cancer patients, with relatively little data specific to men with localised prostate cancer³⁴. Of the data that is available, interventions that include PCa patients undergoing ADT only dominate. Evidence shows that patients undergoing a combined treatment of EBRT+ADT suffer more adverse effects than ADT-only patients. This is particularly true with respect to cancer related fatigue.

ADT

Three RCTs, included in Gardner's review of the "effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy", included fatigue measures⁶³. Bourke et al⁵¹ and Segal *et al*⁶⁵ reported clinically and statistically significant reductions in fatigue with exercise training compared with control⁶³. In contrast, Culos-Reed *et al*³⁹ found no benefits of their home-based intervention with regard to fatigue compared with usual care⁶³.

EBRT+ADT

For several reasons, patients undergoing EBRT+ADT typically experience worse fatigue than patient undergoing ADT only. All four interventions included in this study's review of exercise interventions for PCa patients undergoing EBRT+ADT reported fatigue outcomes. Two supervised aerobic interventions report reductions in fatigue, Monga³⁶ reports a significant reduction of 79%, and Segal³³ reports a non-significant reduction of 11%.

Two home-based aerobic interventions also report reductions in fatigue. Windsor³⁵ reports a significant reduction in fatigue of 82%, Truong³⁴ reports stable mean total fatigue scores from baseline to 6 months post-EBRT FU ($P=0.52$) in the intervention group while fatigue in control subjects escalated from baseline to 6 months post-EBRT ($P \approx 0.3$). Both Windsor and Truong used the BFI questionnaire to estimate fatigue.

Current research

The decline in fatigue in the exercise group in this study is distinct from the rising fatigue scores in the control group which remained elevated at one month post EBRT. In addition trends for higher fatigue interference with six QoL domains were observed in the control group compared with the exercise group (**Satisfying feasibility criteria 6**).

The current intervention demonstrates a mean fatigue reduction of 91% from baseline to 1 month follow-up in the intervention group and a mean fatigue increase of 43% in the control group over the same time period. The mean fatigue score difference from baseline to 1 month follow-up was ($M = -20.17, SD = 15.86$) in the intervention group and ($M = 5.75, SD = 15.30$) in the control group. This difference was statistically significant ($p=.001$). The magnitude of the differences in the means was very large ($\eta^2 = 0.43$)

As in Truong's³⁴ home-based aerobic exercise intervention, higher fatigue interference trends with the 6 QoL domains (general activity, mood, walking ability, normal work/daily chores, relations with others and enjoyment of life) were observed in control compared with exercise group.

Despite patients in the current study receiving higher average doses of radiation at 75 Gy ($SD 3.9$) over a greater average number of fractions 38 ($SD 3.7$), this study has demonstrated comparable and, in most cases, greater reductions in patient fatigue than other ADT or EBRT+ADT supervised or home-based exercise interventions. These improvements remained even after the completion of EBRT and the intervention. This further supports the

recommendation of home-based aerobic exercise as a self-help measure to manage fatigue during and after EBRT³⁴.

HRQoL

Several complimentary interventions have been reported that may help patients cope with cancer and its treatment. Most of these interventions include cognitive behavioural therapies, individual counselling, or psychotherapy and social support³⁶. Meyer and Marks systematic review reports that these types of interventions have no effect of the physical and functional domains of QoL. It is these domains that clinicians consider the most important. Exercise interventions are now seen as the most promising intervention to both maintain and improve PCa patients HRQoL. The current intervention is the first home-based walking intervention to examine and report QoL outcomes.

Four RCTs included in Gardner's review of effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving ADT included QoL measures. Segal et al⁶⁵ demonstrated that resistance training improved PCa-specific QoL, compared with a decline in the control group. Similarly, Galvao et al⁶⁶ found that exercise training was superior for certain components of QoL, including general health, vitality, physical health, sexual activity, cognitive function, fatigue, nausea, and dyspnoea. In contrast, two RCTs^{39,51} observed no significant effects of exercise on general or cancer-specific QoL

Two of the four interventions included in this study's review of exercise interventions for PCa patients undergoing EBRT+ADT reported HRQoL type outcomes. Monga *et al*³⁶ aerobic intervention demonstrated statistically significant improvements in overall QoL (+10%) as well as in the physical (+15%) and social (+14%) domains of QoL using the FACT-P questionnaire compared with a decreases in the control group. Segal *et al*³³ aerobic intervention demonstrated a non-statistically significant increase of 3% in overall QoL using the FACT-P questionnaire.

The current intervention is the first home-based walking intervention to examine and report QoL outcomes. Similar to Monga³⁶ and Segal's³³ supervised interventions above, we employed the FACT-P questionnaire. Our results show that both groups scored similarly at baseline however minor increases in overall QoL, as well as the physical, functional and prostate cancer specific domains of QoL were demonstrated in the exercise group. Control group participants QoL scores remained stable over the same time period. These improvements remained beyond the completion of EBRT and the intervention. This results further support the recommendation of home-based aerobic exercise as a self-help measure to manage maintain and improve HRQoL during and after EBRT³⁴.

Anthropometric Measures

Body composition

ADT alters body composition, substantially increasing abdominal adiposity and decreasing lean body mass within 3 to 12 months of initiation of treatment. This loss of muscle mass is associated with reduced muscular strength, increasing falls and fracture risk, and impairment of physical performance of everyday activities. Furthermore, increased adiposity is also implicated in a range of chronic health problems. There is accumulating evidence suggesting an association between ADT and elevated cardiometabolic risk. This is particularly concerning given that among men with PCa, cardiovascular disease accounts for a proportion of mortality similar to that of PCa itself¹⁸.

This is the first home-based interventions for PCa patients undergoing EBRT+ADT to report a measure of body composition. Exercise interventions for patients undergoing ADT only regularly record body composition measures.

All studies included in Gardner's review, of effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy, included body composition measures. Resistance training seems effective at preserving or even increasing total and regional lean body mass. In fact, no study reported reductions in lean body mass with exercise, despite skeletal muscle loss being a well-documented adverse effect of ADT. Unlike lean body mass, however, most studies did not observe a benefit of exercise regarding measures of adiposity¹⁸.

Only one of the interventions included in this studies review of exercise interventions for PCa patients undergoing EBRT+ADT reported body composition type measures. Similarly to the ADT studies reported above, Segal et al³³ reported that both control and aerobic training groups showed a statistically significant increase in % body fat over 24 weeks. Resistance training participants showed a non-significant decrease in % body fat.

It is possible that previous interventions did not achieve adequate energy expenditure for weight loss. At least 150 minutes per week of moderate-intensity exercise is recommended for weight loss¹⁸. Of note, the three studies in Gardner's review that reported slight reductions in adiposity were among those prescribing higher training volumes¹⁸.

In this study, on average, intervention participants decreased their weight while control participant gained weight. Intervention participants lost M= 1.7 Kg (SD 3.3) from Baseline to 1 MT FU. Control participants gained M=1.7 Kg (SD= 1.7) over the same time period. It also

demonstrates that intervention participants' % body fat decreased while on the intervention however control participants' increased. Intervention participants lost M= 1.1% body fat (SD 2.7) from Baseline to 1 MT FU. Control participants gained M=1.1% body fat (SD= 3.8) over the same time period.

Control participants' waist circumference also increased while intervention participants' decreased. Intervention participants lost M= 0.9cm (SD 2.9) of waist circumference from Baseline to 1 MT FU. Control participants gained M=3.4cm (SD= 3.3) over the same time period.

Muscle mass increases were observed in the intervention groups, in comparison muscle mass decreases were in the intervention group. Intervention participants gained M= 0.5% muscle mass (SD 3.2) from Baseline to 1 MT FU. Control participants lost M=0.8% muscle mass (SD= 3.8) over the same time period

Intervention participants fare better on every objective measure of body composition compared to control participants. This is in contrast to previous aerobic exercise interventions either supervised or home-based. One possible explanation for these positive results is that this study prescribed a 150 min/week of MVPA. This volume of MVPA is recommended for weight loss and is more than in previous aerobic exercise interventions. This exercise was in addition to participants' habitual exercise. We also employed more rigorous measures to ensure adherence.

Bone Health

A recent study by Mennen-Winchell et al⁶⁷ summarises the the effects of ADT on bone health and the public health burden these effects have. The aim of ADT is chemical castration by decreasing patients' testosterone levels below 50 ng/mL to suppress cancer tumour growth. However, this lack of testosterone impairs the cellular replication of new osteoblasts, decreasing bone mineral density BMD and increasing the risk for osteoporosis and bone fracture⁶⁷. During the first year of receiving ADT for prostate cancer, possibly two thirds of men will develop osteopenia or osteoporosis of the hip or spine⁶⁷. BMD can decrease by up to 2.4% and 7.6% during years 1 and 2 of treatment with continuous decrease with each additional year of treatment. In the first year of ADT, fracture risk is 1.5 times greater than the norm, primarily in hip and spine. Recent interventions have demonstrated that BMD can be increased with exercise, which may decrease the risk for osteoporosis fractures. The effects of exercise training on bone health in patients with PCa receiving ADT are yet to be determined¹⁸.

Galvao et al⁶⁸ UCT investigated the effects of exercise on bone health, observing no change in hip BMD or total-body bone mineral content in a single cohort of 10 men after 20 weeks of

resistance training. The authors suggested this result may have represented an attenuation of ADT-induced bone loss.

To the best of the author's knowledge this is the first exercise intervention in PCa patients undergoing ADT+EBRT to report on any aspect of bone health. Participants' bone mass was recorded at each of the four study assessments. There was no change from baseline to one month follow up in either group. However the limitations of the BIA scales to assess bone mass and the short time frame has to be considered. Dual-energy x-ray absorptiometry (Dexa) scans are considered the gold standard and should be considered in the future RCT.

Physical Performance

Decreases in cardiorespiratory and functional fitness are common in men undergoing ADT or EBRT+ADT. These decreases combined with worsening anthropometric measures and fatigue put patients at a higher risk of metabolic syndrome as its associated conditions i.e. cardiovascular disease.

This home-based MVPA exercise intervention improved participants' physical performance. Both groups improved their cardiorespiratory fitness and functional performance from baseline to 1-month follow up. A greater increase was observed in the intervention group.

Cardio respiratory fitness

Cardiorespiratory fitness is a useful diagnostic and prognostic health indicator for patients in clinical settings. It is a strong and independent predictor of all-cause and cardiovascular disease mortality, but its importance is often overlooked. Several prospective studies indicate that CRF is at least as important as the traditional risk factors (hypertension, diabetes, smoking, or obesity), and is often more strongly associated with mortality⁶⁹.

Three of the RCTs included in Gardner's review of the effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy, investigated changes in cardiorespiratory fitness. Bourke et al⁵¹ reported a significant improvement in cardiorespiratory fitness for the exercise group compared with controls⁶³. Similarly, Galvao et al⁶⁶ noted a borderline significant ($P=.080$) between-group difference in 400-m walk time, favouring exercise⁶³. In contrast, Culos-Reed et al³⁹ reported no difference in 6-minute walk test performance between groups⁶³.

Three of the interventions included in this study's review of exercise interventions for PCa patients undergoing EBRT+ADT investigated changes in cardiorespiratory fitness. Segal et al³³ unexpectedly found an statistically significant increase in cardiorespiratory fitness in the

resistance group compared with a smaller non-significant increase in the aerobic group. Monga et al³⁶ and Windsor et al³⁵ also demonstrated statistically significant increases in cardiorespiratory fitness as measured using metabolic equivalents during a treadmill test (METS) and shuttle runs test respectively.

This is the only the second home-based aerobic exercise intervention to include a measure of cardiorespiratory fitness. It is the first intervention to use a standardised 2 minute step test. Both groups of patients in the current study demonstrated almost identical levels of cardiorespiratory fitness at baseline. Unexpectedly, both groups increased their cardiorespiratory fitness from baseline to 1 month follow up. Intervention participants increased their steps by M= 86.7 (SD 62.3) from Baseline to 1 MT FU. This represents an increase of 55.8%. Control participants also increased steps but by M=34.8 (SD= 40.7) over the same time period i.e. an increase of 30 %.

It was surprising to observe the progressive increase in 2-minute step test scores in the control group. Control group patients' anthropometric measures progressively declined from baseline to 1 month follow up. It is reasonable to assume that cardiorespiratory fitness would have followed a similar trend. One potential explanation may be that all patients were hesitant to push themselves to the maximum effort at baseline. We recruited patients at their CT scan and for most patients it was their first real interaction with SLRON staff. As patients became more familiar with the building and staff they may have felt more comfortable completing the test, hence, improving scores from assessment to assessment. It is also reasonable to deduce that intervention participant scores increased by nearly twice that of control participants as a result of the exercise intervention. This increase in cardiorespiratory fitness is consistent with observation from previous supervised aerobic ADT and EBRT+ADT interventions. It is encouraging to observe a similar increase in a simple home-based walking exercise intervention.

Functional Fitness

Intervention patients' improvements in cardiorespiratory were accompanied by improvements in performance of a functional task i.e. 30 sit-stand test. These changes are important because they may contribute to preserving a patient's capacity for independent living. In addition, improvements in functional task performance has been shown to protect against falls and fractures⁶³. Overall, the effects of this home-based exercise intervention on physical performance in EBRT+ADT treated patients with PCa were similar to those observed in more costly supervised interventions⁶³.

Two of the RCTs included in Gardner's review of effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy

investigated changes in functional tasks. Galvao et al⁶⁶ reported superior performance in 6-m walk and 6-m backward walk in the exercise group, with borderline improvement in sit-to-stand performance (P=.074). No between-group differences existed for the 6-m fast-walk or stair-climb task⁶³. Bourke et al⁵¹ also reported better sit-to-stand performance with exercise⁶³.

Only one of the interventions included in this study's review of exercise interventions for PCa patients undergoing EBRT+ADT reported a measure of functional fitness. Monga *et al*³⁶ reported a 15% speed increase in completing the 5 sit-to-stands test (STS).

In contrast to Monga *et al*³⁶ above, in this study participants were asked to complete as many STS as possible in 30 seconds. Intervention participants increased their STS by M= 4.4 (SD 3.5) from Baseline to 1 MT FU. This represents an increase of 25.3%. Control participants also increased steps but by M=1.3 (SD= 3.0) over the same time period i.e. an increase of 9.0 %.

Considering that functional fitness is among the outcomes considered the most clinically significant by clinicians and cancer researchers alike, it is surprising that only three studies of any type included a measure of functional fitness. To the best of the author's knowledge this is the first home-based intervention to include a functional fitness measure. Functional fitness score patterns mirror cardiorespiratory scores above. A similar explanation may also help to explain the increase in control group participant scores from baseline to 1 month follow-up.

It is encouraging to see both measures of physical performance increase in this pragmatic home-based walking exercise intervention considering the importance clinicians attribute to their role in treatment tolerance and recovery.

Intervention Participants Acceptance of the Exercise Intervention

No RCT for patients with prostate cancer receiving androgen-deprivation therapy investigated intervention satisfaction. Only one of the interventions included in this study's review of exercise interventions for PCa patients undergoing EBRT+ADT reported a measure of participants' acceptance of the exercise intervention. Truong et al³⁸ carried out a home-based, 20 minute/day, 3 days/week, 12 week moderate intensity walking intervention. Their intervention was rated as "convenient to extremely convenient" by 73% of intervention participants. Satisfaction was also rated as "good-excellent" by 92% of participants.

In this pilot study, intervention patients gave very positive feedback about their experiences participating in the intervention and were generally clear about the advantages of their involvement in the exercise programme. No intervention participant had an overall negative experience on the trial. One participant did find the recruitment process "upsetting" as he felt we

rushed his CT appointment unnecessarily. He would have preferred to have been recruited at a separate appointment. However upon explanation he understood the logic and necessity to recruit patient at their CT appointment. In general patients had no issues with either the pedometer or the logbook.

Intervention patients' acceptance of the exercise intervention was evaluated using a self-reported questionnaire in addition to in-depth interviews with four participants to elicit information on the subjects' attitude, tolerance and satisfaction with the prescribed exercise.

Intervention participants average convenience and satisfaction scores were 4.8/5 (SD=0.4) i.e. "extremely convenient" and 4.8/5 (SD=0.4) i.e. "extremely satisfied" respectively. It is encouraging to report convenience and satisfaction levels as high as Truong *et al*³⁴, considering that we prescribed 2.5 times the volume of exercise per week and at a greater intensity.

Intervention participants also reported experiencing no pain or discomfort participating in the exercise intervention. Reassuringly, 100% of intervention participant said they would be willing to continue with the intervention independently when they finished EBRT.

Barriers and facilitators

To the best of the author's knowledge this is the first exercise intervention to investigate barriers and facilitators to completing an exercise intervention. The research to date has focused on PCa survivors. The determinants of physical activity in prostate cancer survivors has been most commonly assessed using the Theory of Planned Behaviour-based questionnaires. These studies demonstrated that theory of behaviour constructs, that is, attitude, subjective norms and perceived behavioural control explain a moderate amount of the variance in physical activity intentions, with the intentions being a good predictor of physical activity levels⁷⁰. As the focus of these studies has often been on the perceived physical and psychological benefits of physical activity much less is known about their barriers and facilitators to physical activity⁷⁰.

Recently, Zimmer *et al*⁷⁰ investigated the perceived barriers and facilitators to physical activity in men with prostate cancer. However none of these patients were on an exercise intervention. Facilitators to physical activity for cancer survivors undergoing ADT but not on an exercise intervention included clinician and spousal involvement, personal involvement/ownership of survivorship and group support. Fatigue, pre-existing co-morbidities, increased age and a lack of specific advice from their clinician were cited as barriers⁷⁰.

Two themes emerged as facilitators to completing prescribed exercise. The main facilitator was "convenience". "*The exercise then became part of their daily routine or as one patient put it*

“the walking fitted into my treatment schedule⁵⁸” The second facilitator was “centre environment”. One centre was roughly a 15 minute walk from the train station. Intervention patients’ decided independently to walk to and from the station to accumulate the 30 minutes MVPA, “Coming up on the train was handy because you could walk up from the station, that was 10 minutes or a quarter of an hour out of the way⁶¹” Another centre was located on a nice grounds with lots of green areas that patients took advantage of, *“I chose to do the exercise in the grounds of St Luke’s in Rathgar, which is a Slí na Sláinte 1km per lap. I usually did three laps of that which is 30 minutes. Sometimes I did four⁵⁸”*

Two themes also emerged as barriers to completing prescribed exercise. Time was a common barrier as most patients had to use public transport to get to their treatment centre. However patients appreciated the flexibility of the intervention and managed to fit in the 30 minutes walking at some stage during the day. Poor weather was also a barrier however we provided an indoor route as an alternative. Patients had no issues using the indoor routes throughout the SLRON network.

The above investigation of barriers and facilitators to completing an exercise intervention demonstrate that in a future confirmatory RCT we need to continue to liaise with patients to make the intervention as convenient as possible. The importance of utilising the surrounding environments of each centre to facilitate the exercise has also been highlighted. In contrast, we need to continue to aid patients in planning when and how they will fit the prescribed exercise into their daily schedule. We also need to ensure patients are familiar with alternate indoor routes for use during times of poor weather.

Control Participants Exercise KAP.

This study provides further preliminary evidence that physical activity KAP of PCa patients is poor and exercise advice may not be provided routinely to prostate cancer patients undergoing EBRT+ADT. Control participants walked an average 45900 steps/week while undergoing EBRT. Chippererfield⁷¹ et al 2013 reported that of 356 men with PCa they surveyed, less than half were meeting the National Physical Activity Guidelines of Australia (41.9%). The Irish national physical activity guideline of 10000 steps/day is the same as Australia’s. Unfortunately only 17% of our control patients reached this target.

Clinicians have been described as among the most influential promoters for encouraging behaviour change. The period of transition from a PCa patient to survivor has been described as a ‘teachable moment’, in which people are motivated to make positive lifestyle changes such as increasing MVPA. This period is one that clinicians should optimise without overwhelming the patient with excessive information⁷². Our research further corroborates Zimmer et al⁷⁰, 2014 study outcome that there is a lack of specific advice from their clinician and this acts as barrier to physical activity.

Jones et al⁷³ investigated the attitudes of radiation and medical oncologists in Canada about promoting physical activity to cancer survivors and most respondents agreed that exercise is helpful, important and safe.

Research to date suggests that physical activity is not routinely discussed by clinicians with cancer survivors⁷². Daley et al⁷⁴ investigated the role of medical and clinical oncologists and surgeons in promoting physical activity to breast cancer patients in the U.K. and found that 44.1% of clinicians reported giving physical activity advice routinely. In terms of prostate cancer survivors, research from Australia shows that most prostate cancer survivors do not recall receiving information from clinicians about physical activity⁷⁵. A 2014 study by Spellman et al⁷² reported that although clinicians recognized the benefits of physical activity for their patients, few gave advice about physical activity. Over half of the clinicians (55%) reported that advising patients on physical activity was not part of their role⁷⁵.

Only 33% of patients in the control arm could recall a health care professional discuss the role of exercise during or after EBRT (3 Consultant, 1 Nurse). Subsequently patients had a poor knowledge of exercise. Only 42% of the control group were aware of the correct recommended weekly MVPA guidelines. 33% of control group participants were unaware that MVPA during EBRT may reduce treatment related adverse effect. 58% incorrectly thought that there are genuine safety risks associated with MVPA during EBRT. 92% agreed that exercise could improve HRQoL.

It is worrying that despite their poor exercise knowledge, 100% of the control group felt confident that they knew how to keep physically active (practice) and only 50% were interested in learning more about physical activity (attitude).

Since completing EBRT 67% of intervention participants have not changed their exercise regime. 17% say they have decreased exercise and only 17% say they have increased exercise. This evidence highlights the importance for future research to address the involvement of clinicians and other health care professions in physical activity promotion so that a more complete service is provided.

This pilot study has comfortably satisfied the 6 feasibility criteria that had to be achieved for SLRON to recommend a future confirmatory RCT. The data from this pilot study will serve to inform the design and conduct of a future RCT to confirm the role of a home-based MVPA intervention in improving fatigue, HRQoL, anthropometric measures and physical performance

for patients with prostate cancer undergoing EBRT+ADT. Finally this pilot intervention provides justification for proceeding to a confirmatory trial.

6. LIMITATIONS

Although we feel that our results have many important implications for any future confirmatory RCT and how cancer clinicians prescribe exercise to PCa patients in general, the results and conclusions from this feasibility trial should be interpreted in the context of a number of limitations.

The high rate of compliance and low loss to follow-up may not be achievable in a larger RCT or in clinical practice where the coordinator to participant ratio is decreased.

The absence of more precise anthropometric measures (e.g., DEXA, MRI) limits any conclusions that can be drawn about changes in body composition. Bioelectric impedance analysis (BIA) may not be the ideal method of measuring body composition, since hydration status can affect findings; however, this method of body composition has been used successfully in previous clinical trials with cancer patients and survivors.¹⁴

Participants may have been particularly receptive to exercise particularly walking, creating a self-selection bias and the results may not be applicable to those less amenable to exercise in general or specifically walking.

Pedometers are limited as physical activity measurement devices because they capture movement only of the lower body in the vertical plane and cannot distinguish between walking on different gradients. Although evidence does support a public health recommendation of walking at least 3000 steps in 30 minutes on 5 days each week to help meet current MVPA recommendations. This recommendation should not be used as a precise criterion as pedometer-assessed step rates serve as a proxy for the metabolic equivalent energy expenditure of walking (METs). However, there is substantial error in predicting METs from step rate alone. Rather, it should be used as a public health promotion heuristic to help people lead more active lifestyles⁴⁰.

The sample was based in one large geographical region (Dublin hospitals and their catchment areas) and consisted of predominantly public healthcare patients. The men also appeared relatively physically active and were motivated enough to participate in this study. Thus, future studies in this area may wish to preferentially recruit patients undergoing EBRT+ADT who are not physically active to gain additional insight into their barriers and facilitators to physical activity. Future RCTs should consider longer-term follow up.

Finally, as with the previous four EBRT+ADT exercise intervention studies this study was neither fully blinded nor placebo-controlled; this can be largely explained by the nature of interventions. It is therefore possible that the benefits reported from the intervention were due to experimenter bias, or participant expectancy effects. However every reasonable precaution was taken to minimise such bias.

7. CONCLUSION

This preliminary evidence suggests that a pragmatic home-based MVPA walking exercise intervention is feasible and has the potential to evoke improvements in fatigue, in addition to other important health outcomes in men with PCa undergoing EBRT+ADT.

In Ireland and indeed globally, the incidence of PCa is increasing. In addition, the number of men living as prostate cancer survivors is increasing thanks to improved treatment and management. This simultaneous increase in incidence and survivorship has focused researchers' and clinicians' efforts on improving CRF and HRQoL of both prostate cancer patients under active treatment, and prostate cancer survivors.

Patients with localised prostate cancer undergoing EBRT+ADT in the SLRON experience clinically significant adverse events like CRF and decreased physical and functional capacity that diminish HRQoL and potentially increase the risk for falls related fractures, coronary artery disease, stroke and type-2 diabetes. The public health burden of caring for prostate cancer survivors may therefore become even greater than caring for prostate cancer patients.

Considering the lack of effective pharmacological and complementary treatments, RCT's like the current intervention are needed to confirm the feasibility and efficacy of the most promising solution; moderate to vigorous physical activity (MVPA).

MVPA interventions offset many of the side effects of EBRT and ADT with few side effects itself,^{4,5} however there is limited evidence and consequently a gap in our knowledge regarding the effects of an exercise intervention on treatment-related adverse effects and HRQoL for patients with PCa actively undergoing EBRT+ADT.

Previous research tended to consider only the intervention efficacy and not with the practical issues of RCT feasibility. We know that greater HRQoL benefits for prostate cancer patients have thus far been associated with supervised combined aerobic and resistance facility based interventions, rather than home-based aerobic interventions⁵⁰. The cost and availability of

human resources to provide exercise programs at radiotherapy centres is a barrier that severely limits programme delivery and access⁵⁰. This is particularly relevant in the Irish health system at present. In addition, the patient related obstacles of extra time spent in a hospital per day, extra parking costs and negative treatment experience may reduce participation in a facility-based intervention⁵⁰.

Considering these potential barriers, a home-based aerobic intervention is the preferred option as aerobic exercise is safer and more effective in stimulating long-term changes in exercise behaviour as patients are likely to be more familiar with aerobic exercise such as walking than resistance modalities i.e. weight lifting⁵⁰.

Our research evaluated the feasibility and efficacy of a pragmatic, tailored, moderate to vigorous intensity home-based aerobic exercise intervention for prostate cancer patients actively undergoing EBRT+ADT before proceeding with a confirmatory RCT.

This is the first home based exercise intervention to utilise a pedometer as an objective tool to both encourage and evaluate exercise adherence. It is also the first home based exercise intervention to assess participants' physical performance, and barriers/facilitators to completing exercise while undergoing EBRT.

The exercise intervention group showed greater improvements in fatigue (much greater than anticipated), quality of life, anthropometric measures and physical performance compared to standard care controls. These improvements were sustained beyond the intervention period. Programme convenience and treatment centre environment emerged as exercise facilitators. Intervention participants average convenience and satisfaction scores were 4.8/5 (SD=0.4) i.e. “extremely convenient” and 4.8/5 (SD=0.4) i.e. “extremely satisfied” respectively. A lack of time and poor weather emerged as exercise barriers. Standard care controls had poor exercise KAP post EBRT, e.g. only 42% of the control group were aware of the correct recommended weekly MVPA guidelines.

In conclusion, this study provides evidence that a pragmatic home-based MVPA walking exercise intervention is feasible and has great potential to evoke improvements in fatigue, HRQoL, anthropometric measures and physical performance in PCa patients undergoing EBRT+ADT.

Our results suggest that a future definitive confirmatory RCT should:

- Continue to concentrate on providing an intervention that builds on existing structures and processes in SLRON,

- Utilise each centres' natural environment to provide both indoor and outdoor options should patients wish to complete their exercise independently around treatment times,
- Spend more time exploring with patients how and when to fit exercise into their daily routines,
- Give clearer instructions to coordinators on how to calculate step targets and to patients on how to utilise the logbook and pedometers,
- Research the availability of radio frequency resistant pedometers,
- Consider recruiting more trial coordinators or limit the rate of recruitment,
- Create a Standard Operating Procedure (SOP) with Radiotherapist, Treatment planners and Consultants detailing the management of patient contour reductions of ≥ 1 cm. This should include both imaging and visual inspection guidelines.
- Consider recording physiological measurements i.e. heart rate and blood pressure at each assessment,
- Consider utilising more sophisticated methods to assess bone mass i.e. a DEXA scan.

The researcher can conclude that this intervention is effective and has achieved its: process, resource, management and scientific feasibility criteria and should proceed to a confirmatory RCT with 9 patients per arm to try replicate fatigue effect sizes. Sample size estimates are based on an effect size of 1.67 at 90% statistical power to detect fatigue differences between control and treatment groups using a two-tail two-sample t-test using a 5% significance level. This confirmatory trial should only include two assessment appointments for participants, one at baseline and one at the end of the intervention. If the results of the confirmatory trial replicate the pilot study, SLRON should introduce walking prescriptions into clinical practice.

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9. Appendices

Appendix A

9.1. APPENDIX A: Exercise Study Case Report Form



St. Luke's Radiation Oncology Network
at St. Luke's, Beaumont & St. James's Hospitals



Exercise study case report form

PATIENT NAME _____
 HOSPITAL NUMBER _____ / _____
 CONSULTANT _____
 PUBLIC/PRIVATE _____
 REFERRING CONSULTANT _____

Age _____ (yrs) WHO / KPS _____ Reasons for diagnosis: Screening Symptoms

Date of biopsy _____ / _____ / _____

Perineural Invasion:

Yes No

Not stated

Number of core biopsies positive right side

of cores sampled _____

Number of core biopsies positive left side

of cores sampled _____

Percent of biopsy cores involved with cancer (please tick)

Less than 34% _____ OR 34% or more _____

Highest Gleason Score _____ + _____ = _____

Referring PSA _____ ng/mL SLH PSA Date _____ / _____ / _____ Value: _____ ng/mL

Past Medical History _____

Current Medical History _____

Surgical History _____

Family History _____

Has the patient had a bilateral orchidectomy Yes No

Has the patient had a Hip Replacement Yes No If yes: Left Right Both
(If yes – not eligible for IMRT 08-17 trial)

Does the patient have Ulcerative Colitis Yes No

Any previous treatment for prostate cancer Yes No

Any previous malignancy Yes No Details: _____

Current Medication	Dose	Route	Indication	Start Date	Ongoing
					<input type="checkbox"/>
					<input type="checkbox"/>
					<input type="checkbox"/>
					<input type="checkbox"/>
					<input type="checkbox"/>

Appendix A

Exercise study case report form

Patient Name _____ Hospital Number _____ / _____

PRE TREATMENT ASSESMENT: Please grade using CTC grading 0-4

Diarrhoea	<input type="text"/>	Libido	<input type="text"/>
Constipation	<input type="text"/>	Hot Flashes	<input type="text"/>
Proctitis	<input type="text"/>	Gynaecomastia	<input type="text"/>
Rectal Bleeding	<input type="text"/>	Nocturia (Times/Night)	<input type="text"/>
Bowels (Motions/Day)	<input type="text"/>	Urinary Incontinence	<input type="text"/>
Erectile Dysfunction	<input type="text"/> Any Intervention/medication	Yes <input type="checkbox"/> No <input type="checkbox"/>	If yes specify: _____

SOCIAL HISTORY

Smoker Never Active _____ packs per day _____ yrs smoking Ex smoker

Alcohol Consumption _____ units per week

Any Allergies Yes No If yes: _____

Social Support _____

Is there any psychological, familial, sociological or geographical condition potentially hampering

compliance of treatment Yes No If yes: _____

RECTAL EXAM:

T STAGE PER RECTAL EXAM Nil Felt T1 T1a T1b T1c T2
T2a T2b T3 T3a T3b T4



Details of rectal exam: _____

DIAGNOSTIC TESTS

CXR Yes No Abnormalities Yes No Details _____

BONE SCAN Yes No Abnormalities Yes No Details _____

MRI / CT OF PELVIS Yes No Abnormalities Yes No Details _____

T STAGE PER MRI/CT SCAN: Nil seen T1 T1a T1b T1c T2
T2a T2b T3 T3a T3b T4

FINAL CLINICAL STAGE T N M Date ___ / ___ / ___

Appendix A



St. Luke's Radiation Oncology Network
at St. Luke's, Beaumont & St. James's Hospitals



Exercise study case report form

Patient Name _____ **Hospital Number** _____ / _____

Suitable for

IMRT study	<input type="checkbox"/>	$\geq T3$	Must have <u>one</u> of the following high risk criteria $\geq T3$ \geq Gleason score 8 PSA > 20
Proteomic Analysis study	<input type="checkbox"/>	Not greater than T3 N0 M0	PSA not greater than 20 Gleason Score 7

TREATMENT CHOICE

RADIOTHERAPY	<input type="checkbox"/>	Booking form completed: Yes <input type="checkbox"/> No <input type="checkbox"/> Date completed ____/____/____
HORMONAL THERAPY	<input type="checkbox"/>	

Side Effects of Hormonal Therapy Discussed	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Side Effects of Radiotherapy Discussed	Yes <input type="checkbox"/>	No <input type="checkbox"/>
High Technology Script completed	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Clinical Trial discussed with patient	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Patient Information Leaflet given:	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Patients with one high risk factor consider 6 months of hormones
 Patients with more than one high risk factors consider 3 years of hormones

Duration of hormones prescribed: please tick relevant box:

6 months or 3 years

COMMENTS: _____

Signed: _____ Date: ____/____/____

Appendix A

Acute Toxicity Form – Exercise Study

Please Grade Using CTCAE Version 3.0

WEEK No:	1	2	3	4	5	6	7	8	9
No of Treatments									
DATE	/ /	/ /	/ /	/ /	/ /	/ /	/ /	/ /	/ /
KPS %									
Fatigue									
BOWEL									
Diarrhoea									
Constipation									
Rectal Pain									
Proctitis									
Rectal Bleeding									
Number of BMs/Day									
Mucous Discharge	Yes No <input type="checkbox"/> <input type="checkbox"/>								
BLADDER									
Urgency/ Frequency									
Dysuria									
Haematuria									
Urinary Retention									
Incontinence									
Nocturia (Number per night)									
SKIN									
Radiation Dermatitis									
SEXUAL DYSFUNCTION									
Erectile Dysfunction									
Libido									
HORMONAL TREATMENT									
Gynaecomastia									
Hot Flashes									
Unexpected Event	Yes No <input type="checkbox"/> <input type="checkbox"/>								
If YES: State Event and Grade									

Appendix A



TNM CLASSIFICATION OF PROSTATE CANCER	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour, not palpable or visible by imaging
T1a	Tumour incidental histologic finding in 5% or less of tissue resected
T1b	Tumour incidental histologic finding in 5% or more of tissue resected
T1c	Tumour identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumour confined within prostate
T2a	Tumour involves one lobe
T2b	Tumour involves both lobe
T3	Tumour extends through the prostate capsule
T3a	Tumour extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and /or is fixed to pelvic wall
No	No regional Lymph Nodes
Mo	No distant metastasis
N1/M1	Not to be included, nodes or metastasis present

PERFORMANCE STATUS

KARNOFSKY PERFORMANCE STATUS		WHO PERFORMANCE STATUS	
STATUS	KPS	WHO	STATUS
Normal, No Complaints	100	0	Normal Activity
Able to carry on Normal Activities Minor signs or symptoms of disease	90	1	Symptoms, but fully ambulant
Normal Activity with effort	80	2	Symptomatic but in bed < 50% of the day
Cares for self, unable to carry out on normal activity or do active work	70	3	Needs to be in bed > 50% of the day, but not bedridden
Requires occasional assistance but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50		

Common Toxicity Criteria version 3

ADVERSE EVENT	1	2	3	4
Urinary Incontinence	Occasional (e.g., with coughing, sneezing)	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)
Rectal Bleeding	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., haemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated
Erectile Impotence	Decrease in erectile function (freq/rigidity of erections) but erectile aids not indicated.	Decrease in erectile function (freq/rigidity of erections) but erectile aids indicated	Decrease in erectile function (freq/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	-
Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	-	-
Hot flushes	Mild	Moderate	Interfering with ADL	-
Gynaecomastia	-	Asymptomatic breast enlargement	Asymptomatic breast enlargement; intervention indicated	-
Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL: medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life – threatening consequences (e.g., perforation)
Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period for < 6 weeks	More than daily catheterisation indicated; urological intervention indicated (e.g. TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture) operative intervention requiring organ resection indicated

Appendix B

9.2. APPENDIX B: Brief Fatigue Inventory



St. Luke's Radiation Oncology Network
at St. Luke's, Beaumont & St. James's Hospitals



EXERCISE STUDY

BRIEF FATIGUE INVENTORY

STUDY #: _____

Baseline/Mid RT/End RT/ 1 month F-U

DATE COMPLETED: _____

Appendix B

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

BRIEF FATIGUE INVENTORY QUESTIONNAIRE

Please rate the following using the scale from 0 to 10

1. Please rate your fatigue (weariness, tiredness) by selecting the one number that best describes your fatigue right NOW:

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during the PAST WEEK.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the PAST WEEK.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

4. Circle the one number that describes how, during the past week, fatigue has interfered with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and daily chores)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

9.3. APPENDIX C: Functional Assessment of Cancer Therapy - Prostate



St. Luke's Radiation Oncology Network

at St. Luke's, Beaumont & St. James's Hospitals



EXERCISE STUDY QUALITY OF LIFE QUESTIONNAIRE (FUNCTIONAL ASSESSMENT OF CANCER THERAPY-PROSTATE)

STUDY #: _____

Baseline/Mid RT/End RT/ 1 month F-U

DATE COMPLETED: _____

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

Looking at the above 7 questions, how much would you say your **PHYSICAL WELL-BEING** affects your Quality of life. (Circle one number)

(Not at all) 0 1 2 3 4 5 6 7 8 9 10 (Very much so)

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

Looking at the above 6 questions, how much would you say your **SOCIAL/FAMILY WELL-BEING** affects your Quality of life. (Circle one number)

(Not at all) 0 1 2 3 4 5 6 7 8 9 10 (Very much so)

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

Looking at the above 6 questions, how much would you say your **EMOTIONAL WELL-BEING** affects your Quality of life. (Circle one number)

(Not at all) 0 1 2 3 4 5 6 7 8 9 10 (Very much so)

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

Looking at the above 7 questions, how much would you say your **FUNCTIONAL WELL-BEING** affects your Quality of life. (Circle one number)

(Not at all) 0 1 2 3 4 5 6 7 8 9 10 (Very much so)

9.4. APPENDIX D: Log Book



St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals



EXERCISE STUDY

LOG BOOK

STUDY #: _____

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

The walking programme will consist of walking for 3000 steps in 30 min sessions (**duration**), 5 times per week (**frequency**) at a **MVPA intensity** of 100 steps/min. Sessions should last a minimum of 10 minutes i.e. 3 x10 minute sessions on MVPA days. These steps will be in addition to your usual habitual steps.

Intervention patients: Using your baseline assessment results we have calculated that you should attempt to achieve _____ steps per/day on each of the 5 days in which you carry out the intervention steps. On the other 2 non-intervention days you should attempt to achieve ____ steps/day.

Control group patients: please continue with your normal daily activities and record you steps/week below, ignoring all other columns.

	Week 1 --/-- to --/--		Week 2 --/-- to --/--		Week 3 --/-- to --/--		Week 4 --/-- to --/--		Week 5 --/-- to --/--		Week 6 --/-- to --/--		Week 7 --/-- to --/--	
	Duration of MVPA (mins)	Total Steps/day	Duration (mins)	Total Steps/day										
Monday														
Tuesday														
Wednesday														
Thursday														
Friday														
Saturday														
Sunday														
Total steps/week														

9.5. APPENDIX E: Satisfaction Questionnaire



St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals



EXERCISE STUDY

SATISFACTION QUESTIONNAIRE

STUDY #: _____

Baseline/Mid RT/End RT/ 1 month F-U

DATE COMPLETED: _____



St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals



This questionnaire is for patients who have enrolled in the aerobic exercise study. These questions deal with how you feel towards the exercise program that you were asked to perform.

1. Please circle the amount of pain or discomfort you feel is related to performing exercise (scale 1-5; 1 = no pain or discomfort; 5 = very severe pain or discomfort)

1 2 3 4 5

2. Please circle how convenient the exercise program was for you (scale 1-5; 1 = not convenient, 5 = extremely convenient)

1 2 3 4 5

3. Please give an overall rating of your level of satisfaction with the exercise program (scale 1-5: 1= not satisfied, 2 = fair, 3 = good, 4 = very good, 5= excellent)

1 2 3 4 5

4. Would you be willing to continue with the exercise program after the study is completed?

Yes No Undecided

5. Please provide any additional information or comments you would like us to know about your experience with the exercise program.

6. Did you find the study questionnaires easy to understand and complete?

Yes No (if no please explain)

9.6. APPENDIX F: In-Depth Interview Guide



St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals



EXERCISE STUDY

IN-DEPTH INTERVIEW GUIDE

- Tell me about your experiences participating in the exercise program
- Tell me about when, where and how you attempted the necessary walking
- Was there anything that made the walking easier or harder

9.7. APPENDIX G: Patient Information Leaflet and Informed Consent Form



National Cancer
Control Programme



Fidhmeannacht na Seirbhíse Sláinte
Health Service Executive

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

Patient Information Leaflet and Consent Form

Study Title: Evaluation of the Effects of a Prospective Home-Based Walking Exercise Program on Fatigue and Health Related Quality of Life in Prostate Cancer Patients Undergoing Radiation Therapy: A Pilot study.

Investigator Name: Dr Pierre Thirion, Consultant Radiation Oncologist
Dr Brian O'Neill, Consultant Radiation Oncologist
Mr Ciarán Doyle, Clinical Trial Coordinator

Investigator Address: St Luke's Radiation Oncology Network (SLRON)
- St. Luke's Centre for Radiation Oncology, SLH
- St. Luke's Centre for Radiation Oncology, St. James's Hospital
- St. Luke's Centre for Radiation Oncology, Beaumont Hospital

Introduction:

You are being invited to take part in a Clinical Research Study to evaluate the effects of a home-based walking exercise program on fatigue and health related quality of life in prostate cancer patients undergoing radiation therapy. We will also be monitoring the effect of the exercise programme on body fat, muscle mass, and functional fitness. As this is a new exercise program we are also interested to learn what patients think about the programme. In order to decide whether or not you should agree to be part of this study, it is important for you to understand why the research is being done, what it will involve, as well as the possible risks, benefits and discomforts. This process is known as Informed Consent.

This Patient Information Leaflet gives detailed information about the clinical research study that your doctor and trial coordinator will discuss with you. Please take time to read the following information carefully and make sure you fully understand it. If you would like to know more about something mentioned in this leaflet, or have any questions about this research study, please be sure to ask your doctor or trial coordinator.

Thank you for reading this. Please take your time to decide whether or not you wish to take part.

Background Information

In Ireland, prostate cancer is the second most common cancer in Irish men with an estimated incidence of 3377 cases in 2011. The National Cancer Registry predicts a 275% increase in cases between 2000 and 2020. The number of men living as prostate cancer survivors is also increasing thanks to improved treatment and management.

A diagnosis of prostate cancer and subsequent radiotherapy (RT) and/or androgen deprivation therapy (ADT) regularly causes patients to experience disease- or treatment-related adverse outcomes, such as cancer related fatigue (CRF), which may reduce Health related Quality of Life (HRQoL).

This simultaneous increase in incidence and survivorship coupled with the likelihood of adverse events like CRF has further focused researchers' and clinicians' efforts on improving the health related quality of life (HRQoL) of both prostate cancer patients under active treatment, and prostate cancer survivors.

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

There is strong evidence to suggest that in men with prostate cancer, aerobic exercise interventions may offset many of the side effects of RT and ADT with few side effects itself. Much of the data on this topic has come from intensive, supervised facility-based exercise programs. These studies were not considered convenient by patients who felt they spent enough time in hospital each day receiving their standard treatment, in addition, hospital staff found them labour and cost intensive.

Therefore, there is a need to evaluate the feasibility of pragmatic home-based aerobic exercise interventions and their effects on fatigue and health related quality of life in prostate cancer.

Who is organising the research?

This study is organised by the Clinical Trials Unit at the SLRON.

What is the purpose of the study?

The main aim of the study is to obtain preliminary data on the effects of a home-base walking exercise intervention on fatigue and HRQoL, in patients with localised prostate cancer actively undergoing radical external beam radiotherapy + Androgen Deprivation Therapy (EBRT+ADT).

What will happen during the study?

Participation in this study will in no way influence or alter your prescribed radiation treatment in SLRON. If you agree to participate, you will complete baseline assessments which will be carried out by the trial coordinator. Baseline assessments will consist of self-reported questionnaires on fatigue, HRQoL, and exercise behaviour. An objective measure of functional fitness will be assessed using a standardised sit-stand test. Measures of body fat, height and weight will also be recorded.

Following baseline assessments, you will be randomised to either the control arm (no exercise) or the study arm. This means that neither you nor the study doctor or coordinator can decide which arm you will get, and you have an equal chance of being assigned either arm.

One week after commencing EBRT, participants randomised to the intervention arm will be prescribed a tailored step/week and step/day target. Participants will be asked to walk for a minimum of 3000 steps/day, in 30 min sessions (duration), 5 times/week (frequency) at a rate of 100 steps/minute (MVPA intensity). The minimum time allowed per session is 10 minutes. These 15000 MVPA steps in 150 minutes will be in addition to continuing to achieve your normal steps/day as measured before EBRT. You will record frequency, steps/day and steps/week in an exercise log that will be provided. These steps will be recorded using a pedometer which you must wear during waking hours for the duration of the study. The clinical trial coordinator will meet you weekly to review the exercise log and answer any questions that may arise.

In addition you will also be asked to fill out an exercise satisfaction questionnaire at the start of treatment, once during treatment, after treatment and at 1 month after treatment. You may also be asked to attend an in-depth interview with the study coordinator after completion of your EBRT. This will be your opportunity to tell us what you like and dislike about the exercise programme.

Patients randomised to the control arm will be asked not to join any new formal physical exercise program during the study intervention period. Participants will wear a pedometer and complete a logbook of step/weeks from randomisation to 1 month post EBRT and attend for repeat baseline assessments once during treatment, after treatment and at 1 month after treatment.

How many people will take part in the study?

About 20 patients will take part in the study. 10 participants in each study arm.

St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

There is strong evidence to suggest that in men with prostate cancer, aerobic exercise interventions may offset many of the side effects of RT and ADT with few side effects itself.

Much of the previous data on this topic has come from intensive, supervised facility-based exercise programs. These studies were not considered very convenient by patients who felt they spent enough time in hospital each day receiving their standard treatment, in addition, hospital staff found them labour and cost intensive.

Therefore, there is a need to evaluate the feasibility of pragmatic home-based aerobic exercise interventions and their effects on fatigue and health related quality of life in prostate cancer.

Who is organising the research?

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What is the purpose of the study?

The main aim of the study is to obtain preliminary data on the effects of a home-base walking exercise intervention on fatigue and HRQoL, in patients with localised prostate cancer actively undergoing radical external beam radiotherapy ± Androgen Deprivation Therapy.

What will happen during the study?

Participation in this study will in no way influence or alter your prescribed radiation treatment in SLRON. If you agree to participate, you will complete baseline assessments which will be carried out by the trial coordinator. Baseline assessments will consist of self-reported questionnaires on fatigue, HRQoL, and exercise behaviour. An objective measure of functional fitness will be assessed using a standardised sit-stand test. Measures of body fat, height and weight will also be recorded.

Following baseline assessments, you will be randomised to either the control arm (no exercise) or the study arm. This means that neither you nor the study doctor or coordinator can decide which arm you will get, and you have an equal chance of being assigned either arm.

If you are randomised to the study arm, you will be instructed to walk for at least 30 minutes at a moderate intensity, three days per week starting one week prior to radiotherapy and continuing for the duration of your radiotherapy treatment. You will be required to record the frequency, duration and intensity of your walks in a simple exercise log that will be provided. The clinical trial coordinator will meet you weekly to review the exercise log with you and answer any questions that may arise.

In addition you will also be asked to fill out an exercise satisfaction questionnaire before the start of treatment, once during treatment, after treatment and at 1 month after treatment. You will also be asked to attend an in-depth interview with the study coordinator after completion of your EBRT. This will be your opportunity to tell us what you like and dislike about the exercise programme.

If randomised to the control arm, you will be asked to continue with your treatment as recommended by your consultant and attend for repeat baseline assessments once during treatment, after treatment and at 1 month after treatment.

How many people will take part in the study?

About 20 patients will take part in the study. 10 participants in each study arm.

What do I have to do?

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If randomised to the intervention arm, you need to comply with all instructions given to you regarding the amount walking required and attend for scheduled assessments. If randomised to the control arm, you need to attend for scheduled assessments.

How long will I be on the study?

You will be on the study from one week before radiotherapy treatment until approximately one month after treatment.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign the attached consent form and you will be given a copy of this information leaflet to keep. If you decide to take part but later change your mind, you are free to withdraw at any time without giving a reason. This will not affect the standard of care you receive. Also, your study doctor may decide to withdraw you from the study if it is in your best interest.

What are the alternatives for treatment?

Participating in this study will have no influence or impact on the treatment you receive.

What are the possible side effects of participating in this study?

Your doctor and study coordinator will watch you closely to see if you have side effects. You will be given a physical exam by a member of your oncology team to ensure that you are healthy enough to participate in a walking program. There is a small risk (less than 1%) that you may receive muscular injuries from the walking regimen. There is a small risk (less than 1%) that you may suffer from heart problems due to increased exercise, but this risk is no greater than for the general public.

What are the possible benefits from taking part in this study?

If you agree to take part in this study, there may or may not be a direct benefits to you. You may benefit from increased physical fitness because of the walking exercise program. You may or may not experience reduced fatigue or increased HRQoL with your EBRT. We hope the information learned from this study will help other men with prostate cancer in the future.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, we will tell you or your legally acceptable representative about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study it will have no effect on your care. Also, on receiving new information your Study Doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and your care will continue.

Can I stop being in the study?

Yes, you can decide to stop at any time. Tell the Study Doctor or trial coordinator if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

Withdrawing from this study will have no impact on you radiotherapy treatment.

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Can anyone else stop me from being in the study?

The Study Doctor may stop you from taking part in this study at any time if:

- It is in the best interest for your health
- You experience severe or life-threatening side effects. The study treatment will be stopped if serious side effects develop, and appropriate medical care will be provided
- You do not follow your responsibilities for taking part in the study
- It is discovered at a later time that you do not meet the study participation requirements
- You need treatment not allowed in the study
- Your disease becomes worse during treatment to the extent that you are unable to complete treatment, you will be told and the treatment will be stopped. Other medical care will be discussed with you
- Administrative reasons require your withdrawal

What happens if I am injured because I took part in this study?

It is important to note that nothing said in this consent form alters your legal rights to seek to recover damages should injury be suffered as a result of participation in this study. Every reasonable precaution will be taken to ensure your safety during the course of the study.

Will my taking part in this study be kept confidential?

Every effort will be made to ensure that the personal information in your medical record will be kept private. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The information collected, as part of this study will be shared with other researchers and Doctors. This study is being carried out in partial fulfilment of a Doctorate in Public Health at the London School of Hygiene and Tropical Medicine.

What are the costs of taking part in this study?

You will not be charged for the cost of tests done for the purpose of this study. You will not be paid for your participation in this study. Your travel expenses will not be reimbursed.

Who has reviewed and approved this study?

This study has been approved by St. Luke's Radiation Oncology Network Research Ethics Committee.

Contact for further information

If you have any questions concerning the procedures of this study, or if any problems arise during the Clinical Research Study, you should contact the following people:

Study Doctor Name: Dr Pierre Thirion Tel: 01- 406 5000

Clinical trial coordinator: Ciarán Doyle MSc Tel: 01- 406 5466

For questions about your rights or if you wish to make a complaint while taking part in this study, call the Corporate Services Officer at 01 406 5000 and your complaint will be dealt with promptly.



St. Luke's Radiation Oncology Network at St. Luke's, Beaumont & St. James's Hospitals

INFORMED CONSENT FORM

Study Title: Evaluation of the Effects of a Prospective Home-Based Walking Exercise Program on Fatigue and Health Related Quality of Life in Prostate Cancer Patients Undergoing Radiation Therapy: A feasibility study.

Study Doctor Name: Dr Pierre Thirion

Hospital name: St. Luke's Radiation Oncology Network

Please Initial box

1. I confirm that I have been given a copy of all 5 pages of the Patient Information Leaflet and Consent Form. I have read the Patient Information Leaflet and Consent Form or it has been read to me. This information was explained to me and my questions were answered
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and without my medical care or legal rights being affected
3. I understand that data related to me collected during this study will be processed and analysed as is required by this clinical study and according to the Data Protection Act
5. I agree to my GP being informed of my involvement in this study
6. I agree to take part in this evaluation of the effects of a prospective home-based walking exercise program on fatigue and health related quality of life in prostate cancer patients undergoing radiation therapy

Name of Patient (Print)

Signature of Patient

Date

Name of Witness (Print)
(IF APPLICABLE)

Signature of Witness

Date

Name of Investigator (Print)

Signature of Investigator

Date

Name of trial coordinator

Signature of trial coordinator

Date

9.8. APPENDIX H: Key Informant Interview Guide for Trial Co-ordinators



**St. Luke's Radiation Oncology Network
at St. Luke's, Beaumont & St. James's Hospitals**

**Process, resource and management
Trial Co-ordinator Key Informant Interview guide**

1. Process
 - a. Did you find the inclusion/exclusion criteria too restrictive
 - b. How did you find the study assessment tools, how do you feel patients found them
2. Resources
 - a. Tell me about equipment and room availability
 - b. How do you think you centre coped with the trial and extra patient assessments.
 - c. Did you have any problem meeting the assessment requirements
 - d. Do you envisage any issue rolling out this pilot study into a larger RCT
3. Management
 - a. Tell me about any trial management issues at this site
 - b. Tell me about data entry. Problems?
 - c. Do you think there are any other data values which we have forgotten?

Are there any other issue which you would like to discuss in relation to this pilot study or the larger RCT.

9.9. APPENDIX I: Control Group Physical Activity KAP



**St. Luke's Radiation Oncology Network
at St. Luke's, Beaumont & St. James's Hospitals**

Exercise Knowledge, Attitude and Practices.

Knowledge

1. The Irish national guidelines for moderate to vigorous physical activity recommend adults should exercise for
 - i. 10-30 minutes per week
 - ii. 30 -60 minutes per week
 - iii. 60-90 minutes per week
 - iv. 90+ minutes per week
2. Regular physical activity is associated with reduced effects of treatment for example fatigue.
(Please circle one answer)

Strongly Agree – Agree- Neither agree or disagree-Disagree, Strongly Disagree- Unsure

3. Regular physical activity can improve your quality of life during and after treatment
(Please circle one answer)

Strongly Agree – Agree- Neither agree or disagree-Disagree, Strongly Disagree- Unsure

4. There are some risks for patients participating in regular physical activity during and after treatment. (Please circle one answer)

Strongly Agree – Agree- Neither agree or disagree-Disagree, Strongly Disagree- Unsure

Attitude

1. I feel confident that I know how to keep physically active
(Please circle one answer)

Strongly Agree – Agree- Neither agree or disagree-Disagree, Strongly Disagree- Unsure

2. I would like to know more about physical activity
(Please circle one answer)

Strongly Agree – Agree- Neither agree or disagree-Disagree, Strongly Disagree- Unsure

Practices

1. Were you advised to exercise by any member of your healthcare team since being diagnosed with prostate cancer? (Please explain who advised you and what they recommended and why)

2. Have you exercised since being diagnosed with prostate cancer? (Please tell us about this exercise)

9.10. APPENDIX J: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

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16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

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25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

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31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.