The Role of Physical Activity for Patients with Advanced Cancer

Gráinne Sheill

BSc., MSc., MISCP

Submitted for the degree of Doctor in Philosophy

University of Dublin, Trinity College
Discipline of Physiotherapy
School of Medicine

March 2018

Declaration

This thesis is submitted by the undersigned to Trinity College Dublin for the examination of the degree in Doctor of Philosophy. All work described herein is entirely my own work and has not been submitted as an exercise for a degree at this or any other University. I hereby agree that this thesis may be lent or copied upon request with the consent of the librarian and with the due acknowledgement of the author.

Gráinne Sheill 09/04/2018

Summary

The benefits of exercise for people living with cancer are well established. In advanced disease, there is a need to examine the potential physical and psychological benefits of engaging in physical activity. The aim of this thesis was to explore the role of physical activity for people living with advanced stages of cancer using quantitative and qualitative methods.

Work for this thesis commenced with a narrative review regarding exercise prescription for patients with bone metastases (Chapter 1). Exercise interventions were associated with positive physical and self-reported outcomes in patients with bone metastases. No association was found between exercise and fracture risk; however, the need to individualize exercise prescription and adapt exercises to patient ability were reinforced in all papers reviewed. While exercise prescription to patients with bone metastases does involve complex decision making, a number of tools are outlined in this review to inform both the assessment of patients and the prescription of exercise. A systematic review of exercise trials involving patients with advanced cancer (Chapter 3) found that recruitment, adherence and attrition rates varied widely among the studies reviewed. Additionally, definitions and the measurement of exercise adherence varied widely. With increasing evidence supporting the safety and efficacy of exercise training in oncology patients with advanced and complex presentations, concentrated efforts are needed to increase the numbers of patients with advanced cancer, including those with metastatic cancer, recruited to exercise programmes and to ensure patients recruited are representative of clinical practice.

Further studies in this thesis (Chapters 5a and 5b) explored the views of clinicians and physiotherapists in Ireland towards physical activity for patients with advanced cancer. Both groups felt physical activity is safe and important for this population. However, both groups demonstrated a need for further education in the area of physical activity and advanced disease. Similarly, an additional study found patients also have a need for further information regarding physical activity following diagnosis (Chapter 4). Some of the challenges to implementing this into clinical practice were highlighted by clinicians and physiotherapists, who reported many concerns regarding physical activity in the advanced cancer population. These concerns centred on a risk of pathological fracture and a risk of spinal cord compression. Patients were perceived by physiotherapists as highly susceptible to injury due to their advanced stage of disease. This is a significant issue for patients with advanced stages of disease. There is, however, evidence that carefully designed physical activity programmes can be safely introduced for patients

with many symptoms of advanced disease, including bone metastases (Chapter 1). Many patients in Chapter 4 reported a decrease in physical activity levels following a diagnosis of advanced cancer and did not identify common 'cues to action' post-diagnosis that prompted them to maintain or increase their physical activity level, such as written information about physical activity or referral for exercise consultations. This issue was also highlighted by physiotherapists in Chapter 5a, who felt patients with advanced cancer have limited exposure to factors that may prompt the maintenance or an increase in physical activity levels. There is a need to increase 'cues to action' or prompts which encourage patients with advanced cancer to engage in physical activity. These cues to action may take the form of verbal prompts from healthcare staff to encourage physical activity or visual cues such as pamphlets or posters which focus on the benefits of physical activity. Recent evidence on the benefits of physical activity for patients with advanced disease should be disseminated widely to healthcare professionals. This may encourage discussion around exercise during hospital consultation and the introduction of exercise rehabilitation referrals as a part of the standard care of patients with advanced cancer.

A number of barriers to engaging patients with advanced disease in physical activity are identified in Chapters 3 and 4. Firstly, narrow inclusion criteria for exercise clinical trials restricts the number of patients with advanced cancer who are eligible for studies involving physical activity interventions. Inclusion criteria often includes narrow prognostic criteria or measures of functional performance, excluding many patients with advanced cancer. Broadening inclusion criteria may increase the recruitment rates to physical activity programmes. This would ensure patients recruited represent the advanced cancer population found daily in clinical practice. Additionally, although patients did not report a cancer diagnosis as a barrier to physical activity, many symptoms of advanced disease, such as pain and fatigue, were identified are barriers to these patients participating in physical activity (Chapter 4). Referral to an exercise specialist should be considered for these patients. Exercise specialists can prescribe tailored physical activity programmes which consider patients' individual barriers to exercise. Indeed, the ExPeCT Trial (Chapter 6) introduced an individualised exercise programme for patients with metastatic prostate cancer. This trial demonstrated that a progressive aerobic exercise programme can be introduced to patients living with metastatic prostate cancer in a multicentre setting. Although the results of the programme did not result in significant changes in psycho-social self-report measures, the exercise intervention was well tolerated by participants and did not result in any adverse events, laying the foundation for further trials in this population.

Acknowledgements

I would like to thank my supervisors on this project, Prof. Julliette Hussey, Prof. David Hevey and Prof. Stephen Finn for their support and guidance over the past number of years. I would also like to thank Niamh Murphy, physiotherapy manager in St. James's Hospital, for her encouragement to start this project and her support throughout. To the staff in the Clinical Research Facility in St. James's, I owe a huge amount. I would also like to thank all of the Cancer Trials Ireland nurses for their help with recruitment. Finally, to Dr Emer Guinan, who has championed all of this work from the very beginning and has been there every step of the way, thank you. I really would not have made it to this point without your guidance, support and friendship.

To Lauren, I couldn't have shared the last few years with anyone better. To Ann-Marie, thank you for being so generous with your time and looking out for me from the moment you arrived! To all of the members of the research room during my time, thank you for your advice and encouragement.

To all of the patients who participated in these studies. Thank you for being so giving with your time and being so willing to take part in research.

Finally, to my friends and family. To my parents Caroline and Billy, who have always supported me through all of my endeavours, I owe so much to you. To my grandparents, who have encouraged me from Tipperary over the last four years, thank you. To my brother and sister, who have provided much needed laughs and jokes, and to my friends, who could not have been more understanding of my journey over the past few years, I appreciate you all so much. And finally, to Cian, for all his never-ending support and reassurance over the years – there are no words. I can't wait to start our next adventure.

.

Table of Contents

List of Figures

List of Tables

List of Appendices

Abbreviations

ACSM: American College of Sports Medicine

ADT: Androgen Deprivation Therapy

Adv: Advanced

AI: Aerobic Intensity

BMI: Body Mass Index

BTP: Breakthrough Pain

CRP: C-Reactive Protein

CT: Computed Tomography

CTCs: Circulating Tumour Cells

DRE: Digital Rectal Examination

EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

ExPeCT: Exercise, Prostate Cancer and Circulating Tumour Cells

FACT P: Functional Assessment of Cancer Therapy - Prostate

F: Frequency

FI: Flexibility Intervention

GLSIQ: Godin Leisure Score Index Questionnaire

HADS: Hospital Anxiety and Depression Scale

HBM: Health Belief Model

HR: Heart Rate

HRPC: Hormone Refractory Prostate Cancer

HRR: Heart Rate Reserve

HRQOL: Health Related Quality of Life

I: Intensity

ICH GCP: International Conference on Harmonisation Good Clinical Practice

IL-6: Interleukin 6

LHRH: luteinizing hormone-releasing hormone

Mins: Minutes

MRI: Magnetic Resonance Imaging

MS: Metabolic Syndrome

MSCC: Metastatic Spinal Cord Compression

MTSS: Musculoskeletal Tumour Society Score

NCB: Needle Core Biopsy

NK: Natural Killer

OMED: Oral morphine equivalent dose

PA: Physical Activity

PDGF: Platelet-Derived Growth Factor

PHR: Peak Heart Rate

PI: Principal Investigator

PIN: Participant Identifier Number

PrCa: Prostate Cancer

PSA: Prostate Specific Antigen

QoL: Quality of Life

RCT: Randomised Controlled Trial

RI: Resistance Intensity

RM: Repetition Max

RNA: Ribonucleic Acid

RPE: Rate of Perceived Exertion

RPE: Rate of perceived exertion

SD: Standard Deviation

s.e.: Standard Error

SRE: Skeletal Related Event

STS: Sit to Stand

T: Time

T0: Baseline

T3: Three months

T6: Six months

TNFα: Tumour Necrosis Factor Alpha

TUG: Timed up and Go

Ty: Type of Exercise

UK: United Kingdom

VAS: Visual Analogue Scale

WHO: World Health Organisation

6MWT: Six minute walk test

Publications from the work in this Thesis

Published Papers

Sheill, G., Brady, L., Guinan, E., Hayes, B., Casey, O., Greene, J., Vlajnic, T., Cahill, F., Van Hemelrijck, M., Peat, N. and Rudman, S., 2017. The ExPeCT (Examining Exercise, Prostate Cancer and Circulating Tumour Cells) trial: study protocol for a randomised controlled trial. *Trials*, *18*(1), p.456.

Sheill, G., Guinan, E., Neill, L.O., Hevey, D. and Hussey, J., 2017. The views of patients with metastatic prostate cancer towards physical activity: a qualitative exploration. *Supportive Care in Cancer*, pp.1-8.

Sheill, G., Guinan, E., O Neill, L.O, Hevey, D. and Hussey, J., 2018. Physical activity and advanced cancer: The views of chartered physiotherapists in Ireland. *Physiotherapy theory and practice*, pp.1-8.

Sheill, G., Guinan, E., Neill, L.O., Hevey, D. and Hussey, J., 2017. Physical activity and advanced cancer: the views of oncology and palliative care physicians in Ireland. *Irish Journal of Medical Science (1971-)*, pp.1-6.

Manuscripts in press:

Sheill, G., Guinan, E.M., Peat, N. and Hussey, J., 2018. Considerations for Exercise Prescription in Patients with Bone Metastases: A Comprehensive Narrative Review. *PM&R*.

Published Clinical Article

Exercise as treatment to improve prostate cancer morbidity and mortality *Cancer Professional* (Volume 10 Issue 2).

Manuscripts under review:

G. Sheill, E. Guinan, D. Hevey, L. Brady, J. Hussey. (2018) Systematic Review: Exercise interventions for patients with advanced cancer: Recruitment, Attrition and Adherence. Manuscript submitted for review in the Journal of Supportive and Palliative Care.

1. Chapter 1: Introduction

This thesis will explore the role of physical activity for patients with advanced cancer. Chapter 3, Chapter 4 and Chapter 5 relate to all patients with advanced cancer, while Chapter 6 relates specifically to patients living with advanced prostate cancer. For this reason the following chapter introduces both prostate cancer and advanced cancer.

1.1. Prostate Cancer

1.1.1. The Prostate and Prostate Cancer

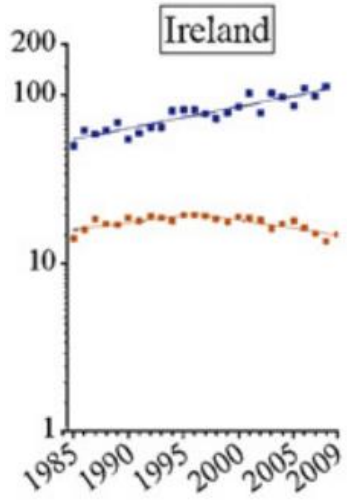
The prostate gland is a small gland found only in men and is part of the male reproductive system. It is the size of a walnut and surrounds the first part of the urethra which carries urine from the bladder to the penis. The prostate lies close to the rectum through which it can be closely felt and examined for its size. The function of the prostate is to make some of the fluid used to carry sperm.

Prostate cancer is cancer of the prostate gland. Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body's cells begin to divide without stopping and spread into surrounding tissues. Cancerous tumours are malignant, which means they can spread into, or invade, nearby tissues (National Cancer Institute, 2017). More than 99% of prostate cancers develop in the gland cells within the prostate. This type of prostate cancer is called adenocarcinoma.

1.1.2. Prostate Cancer Incidence and Aetiology

Prostate Cancer is the most common cancer found in men in the developed world (Ferlay *et al.*, 2010). It is the second most commonly diagnosed cancer in Ireland, accounting for 15.6% of all cancer diagnosis from 2015-2017 (National Cancer Registry, 2017). This equates to over 3,400 men receiving a diagnosis of prostate cancer each year, with trends showing increasing incidence and decreasing mortality rates (Center *et al.*, 2012) (Figure 1). Advanced age is the leading risk factor for prostate cancer. The median age at diagnosis is 66 years however 69% of deaths occur in men aged ≥75 years (Droz *et al.*, 2017). As the population ages, so will the number of prostate cancer diagnoses (Dunn and Kazer, 2011). Race is the second most common risk factor for developing prostate cancer. African-American men are at greatest risk for developing prostate

cancer, with a lifetime probability of developing prostate cancer of 18.25%, compared to 15.25% for Caucasian men. Many exogenous risk factors also exist, including diet and environmental agents. For example, fat consumption, especially polyunsaturated fat, shows a strong, positive correlation with prostate cancer incidence and mortality (Bostwick *et al.*, 2004). Many of the identified prostate cancer risk factors do not adequately explain risk in black men, however, racial differences in prostate cancer risk may be explained by racial variation in the insulin-like growth factor system and its influence on height (Layne et al. 2018). Total physical activity has not been found to relate to prostate cancer risk among white men. However, among black men, frequent physical activity of a moderate to vigorous intensity during young adulthood (i.e. ages 19 to 29 years) is related to a statistically significant 35% reduction in prostate cancer risk (Moore *et al.*, 2009). The relationship among obesity, its physiologic sequelae, and the risk of prostate cancer is unclear. Results of studies examining body mass index (BMI) and prostate cancer risk are conflicting. However, larger studies, notably the Cancer Prevention Studies of the American Cancer Society, have consistently demonstrated that obese men have a significantly greater chance of dying of prostate cancer than non-obese men (Freedland and Aronson, 2004).



Blue = Incidence

Orange = Mortality

Figure 1 Trends in Irish Prostate Cancer Incidence and Mortality Rates

(Center et al., 2012)

1.1.3. Prostate Cancer Symptoms

Prostate cancer has no symptoms in its early stage. Symptoms often develop after the cancer has travelled outside of the prostate. Because of the proximity of the prostate gland in relation to the bladder and urethra, prostate cancer may be accompanied by a variety of urinary symptoms. These may include, dysuria, urgency, frequency, nocturia, hesitancy, difficulty with weak or intermittent flow, feeling that the bladder has not emptied or blood present in the urine. Less common symptoms include trouble having or keeping an erection and lower back pain or pain in the hips or upper thighs.

1.1.4. Prostate Cancer Diagnosis and Staging

Cancer staging describes the severity of an individual's cancer based on the magnitude of the original (primary) tumour as well as the extent to which the cancer has spread in the body. Understanding the stage of the cancer determines prognosis and treatment plan for individual patients. Prostate cancer can be divided into 4 stages: disease localised to the prostate gland (Stage I); locally advanced disease with cancer in more than half of one side of the prostate but still completely contained within the prostate gland (Stage II); primary metastatic disease which may have spread to nearly seminal vesicles (Stage III); and hormone refractory prostate cancer (HRPC) or metastatic castration resistant prostate cancer (Stage IV). The latter describes prostate cancer which keeps growing even when the amount of testosterone in the body is reduced to very low levels.

Evidence for an involvement of sex steroids in disease progression is overwhelming in prostate cancer and this persists in many cases after relapse, when initial anti-hormonal therapies have failed. Around 75% of metastatic prostate cancers are hormone sensitive, with the average time for response to androgen (hormone) deprivation estimated at 18 months (Auclerc *et al.*, 2000). A sub-group of patients, who after being managed by androgen deprivation, have an increasing prostate specific antigen level in the absence of obvious clinical disease progression, are described as "hormone refractory" at an earlier state of the disease continuum. This stage can manifest with or without skeletal metastases and patients may have a very different disease course compared to patients traditionally diagnosed with prostate cancer (Lindqvist *et al.*, 2006, Chang, 2007) (Figure 2).

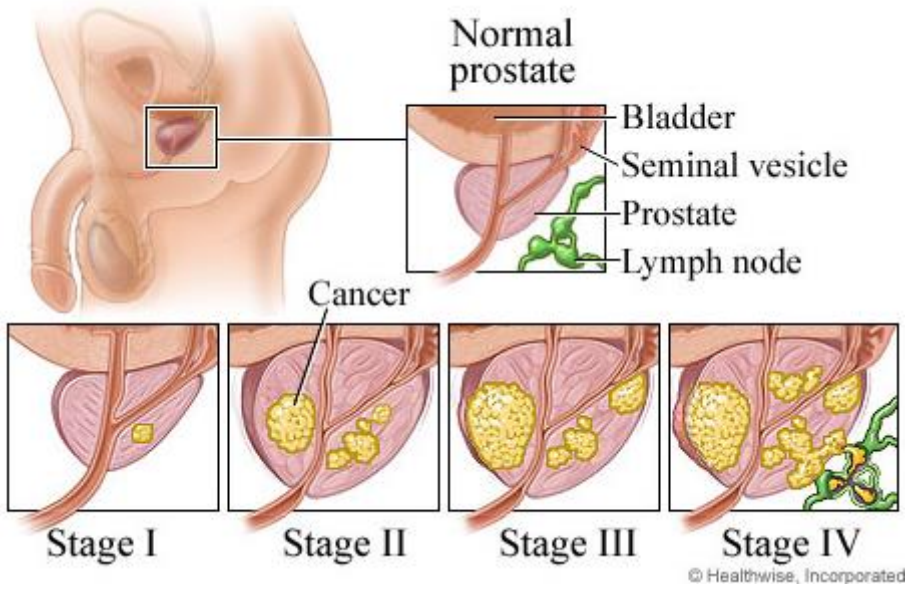


Figure 2 Prostate cancer progression from Stage I-Stage IV

The clinical staging of prostate cancer was devised from the American Joint Committee on Cancer (AJCC) tumour, node and metastasis (TNM) system (Table I). In the TNM system the T refers to the size and extent of the main tumour. The main tumour is usually called the primary tumour. The N refers the number of nearby lymph nodes that have cancer. The M refers to whether the cancer has metastasised. In comparison the Jewett-Whitmore staging system has four stages. Stages A and B are considered curable. The C and D stages are treatable, but their prognosis is not encouraging. In addition, a number is assigned to describe more specifically each Stage. For example, a tumour classified as phase B1 is a single nodule of the tumour limited to a lobe of the prostate.

	AJCC Prostate Cancer Stage Groupings													
	Stage I		Stage IIa				Stage IIb			III	Stage IV			
Jewett-Whitmore stage	A1		A2, B0-2							C1-3	D1		D2	
TNM stage	T1a-c N0M0	T2a N0M0	T1a-c N0M0	T1a-c N0M0	T2a N0M0	T2a N0M0	T2b N0M0	T2c N0M0	T1-2 N0M0	T1-2 N0M0	T3a-b N0M0	T4 N0M0	Any T N1M0	Any T Any N M1
Gleason score	≤ 6	≤ 6	7	≤ 6	≤ 6	7	≤ 7	Any	Any	≥ 8	Any	Any	Any	Any
PSA level (ng/ml)	< 10	< 10	< 20	10-19.9	10-19.9	< 20	< 20	Any	≥ 20	Any	Any	Any	Any	Any

Table I The American Joint Committee on Cancer Stage Groupings.

Once the T, N, and M are determined, they are combined, and an overall stage of 0, I, II, III, IV is assigned. Sometimes these stages are subdivided as well, using letters such as IIIA and IIIB. In some cancer types such as prostate cancer non-anatomic factors are required for assigning the anatomic stage/prognostic group. e.g. Gleason Score. These factors are collected separately from T, N, and M, which remain purely anatomic, and are used to assign stage groups.

Prostate-specific antigen, or PSA, is a protein produced by normal, as well as malignant, cells of the prostate gland. The PSA test measures the level of PSA in a man's blood. There is no specific normal or abnormal level of PSA in the blood, and levels may vary over time in the same man. In the past, PSA levels of 4.0 ng/mL and lower were considered as normal however more recent studies have shown that some men with PSA levels below 4.0 ng/mL have prostate cancer and that many men with higher levels do not have prostate cancer (Thompson *et al.,* 2004). If PSA levels rise or a suspicious lump is detected during a digital rectal exam, the doctor may recommend additional tests such as a prostate biopsy, however two out of three men with a raised PSA who proceed to prostate biopsy do not have prostate cancer and in about 18% of patients, prostate cancer is detected by a suspect DRE alone, irrespective of the PSA level (Richie *et al.,* 1993). Transrectal ultrasound-guided needle biopsy is the most widely used method for obtaining prostatic tissue (Dunn and Kazer, 2011). The diagnosis of prostate cancer is accomplished by a histologic evaluation of prostate tissue sampled from a prostate needle biopsy. The Gleason grading system of adenocarcinoma of the prostate is an established prognostic indicator. This grading system is based entirely on the histologic pattern of arrangement of carcinoma cells in sections of prostate biopsies. Five basic grade patterns are used to generate a histologic score, which can range from 2 to 10. It has been recognised that the grade of a neoplasm is related to its malignant potential (Humphrey, 2004). An isotope bone scan is recommended for patients with

prostate cancer with a Gleason score ≥8, PSA >20µg/L or stage ≥T3, regardless of serum PSA (Department of Health, 2015).

1.1.5. Prostate Cancer Prognosis

Between 2008 and 2012 in Ireland, survival rates at one year post-prostate cancer diagnosis was 99% for those with Stage I disease, compared to 78% for those diagnosed with Stage IV disease. Survival rates at five years after diagnosis fall to 93% for those diagnosed with Stage I disease compared to 38% for those diagnosed with Stage IV cancer (National Cancer Registry, 2017) (Figure 3). The median survival after the development of hormone-refractory disease is approximately 40 months in patients with evidence of skeletal metastasis and 68 months in those without skeletal metastasis (Oefelein *et al.*, 2004). Advances in systemic therapies for cancer have prolonged survival even in those who cannot be cured, and many people now live with advanced stages of prostate cancer for longer periods (Conte and Coleman, 2004, Palumbo *et al.*, 2013).

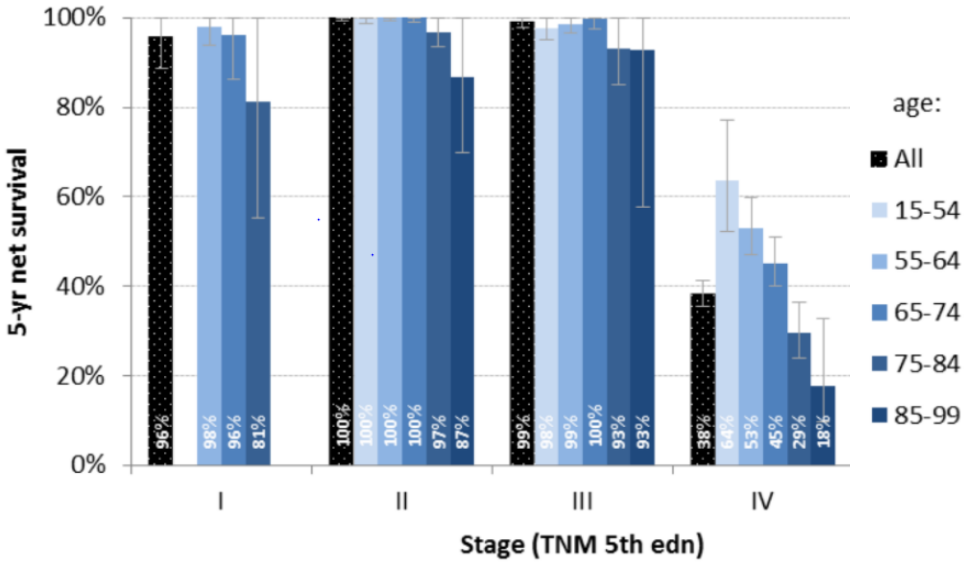


Figure 3: 5-year net survival for prostate cancer by stage at diagnosis.

Overall (not age-standardized) and by age-group figures given for 2010-2014 (National Cancer Registry, 2017)

1.2. Advanced Cancer

A cancer that has spread from the place where it first started to another place in the body through the blood or the lymph system is called metastatic cancer. A cancer which cannot be cured or controlled with treatment is often called advanced and the terms metastatic and advanced are often used interchangeably. At the end of 2015, there were an estimated 15,271 people living with Stage IV metastatic or advanced cancer in Ireland (Irish National Cancer Registry, Table II).

Age at end 2015	Females	Males	Total
<30	222	259	481
30-49	1,006	938	1,944
50-69	3,302	3,287	6,589
70+	2,782	3,475	6,257
Total	**7,312**	**7,959**	**15,271**

Table II Numbers of living cancer patients diagnosed with stage IV/Metastatic Cancer in Ireland at the end of 2015.

The process by which cancer cells spread to other parts of the body is called metastasis (Amercian Cancer Society, 2016). Metastasis is a multi-step process encompassing the (i) local infiltration of tumour cells into the adjacent tissue, (ii) transendothelial migration of cancer cells into vessels known as intravasation, (iii) survival in the circulatory system, (iv) extravasation and (v) subsequent proliferation in competent organs leading to colonization (Eger and Mikulits, 2005), (Figure 4). Cancer can metastasise to almost any part of the body, although different types of cancer are more likely to spread to certain areas than others. For example, prostate, breast and bladder cancer commonly spread to the bone.

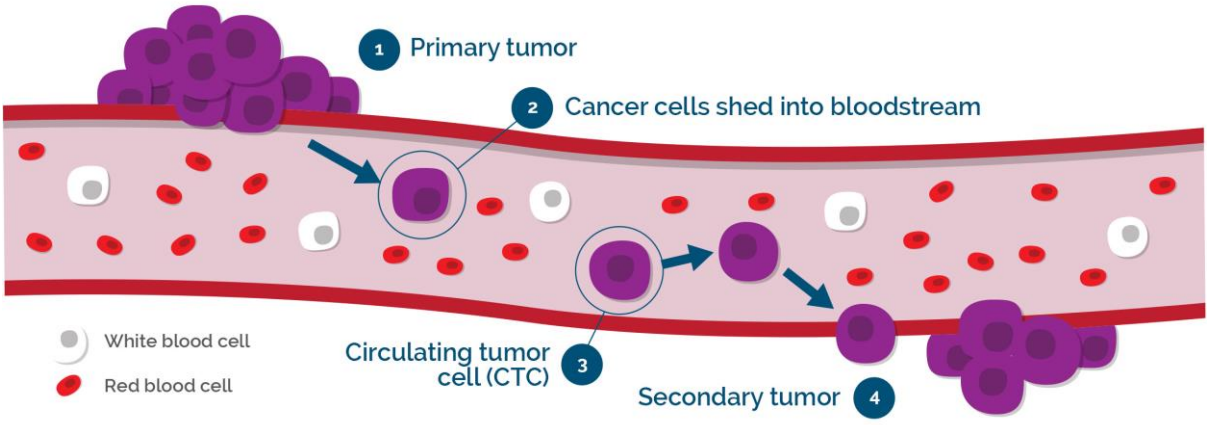


Figure 4 Metastases of primary tumour cells

Persons with advanced cancer are polysymptomatic. Symptom prevalence is affected independently by age, gender, and performance status. The effect of age is unidirectional, unlike gender or performance status (Walsh *et al.*, 2000a). A study of 1,000 patients referred to the Palliative Medicine Program of the Cleveland Clinic reported that pain, easy fatigue, weakness, anorexia, lack of energy, dry mouth, constipation, early satiety, dyspnoea, and >10% weight loss were the most prevalent patient-reported symptoms. The prevalence of these 10 symptoms ranged from 50% to 84% (Walsh *et al.*, 2000a). Patients with higher (worse) performance status scores were more likely to experience confusion, sedation, blackouts, hallucinations, weakness, mucositis, anorexia, memory problems, dry mouth and constipation. Many patients with advanced cancer experience symptom clusters, defined as groups of two or more concurrent symptoms that co-occur independently of other clusters, which may or may not share a common aetiology (Dodd *et al.*, 2001). For example, symptoms of pain, depression, and fatigue have been found to cluster in cachexic patients living with advanced cancer (Laird et. al. 2011). Symptom clusters are predictive of compromised patient outcomes such as poor quality of life (QOL) and low functional status (Dong *et al.*, 2014, Laird et al. 2011). For example, an emotional cluster, (tense-worry-irritable-depressed) has proven to be the strongest predictor of overall quality of life in advanced cancer patients, while clusters including fatigue/pain are a stronger predictor of overall health (Dong et al. 2016).

1.2.1. Advanced Prostate Cancer

About 10% to 20% of men with prostate cancer present with metastatic disease, and in many others, metastases develop despite treatment with surgery or radiotherapy (Tannock *et al.*, 2004). Prostate cancer that has spread through the bloodstream most often spreads firstly to the bones, then to the lungs and liver. Primary tumour cells generally metastasise to active hematopoietic bone marrow tissue in skeletal areas with high proportions of trabecular bone, such as the skull, spine, pelvis, femur, and humerus. These bone lesions lead to a structural weakening of bone which is independently associated with higher risk of subsequent skeletal related events, disease progression and death (Conte and Coleman, 2004, Chintalacharuvu *et al.*, 2011, Lee *et al.*, 2011). Skeletal events may include pathological fracture and metastatic spinal cord compression (MSCC). MSCC is defined as spinal cord or cauda equine compression by direct pressure or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability (NICE, 2008). MSCC occurs in 5% to 14% of all patients with cancer during the course of their disease (Rades *et al.*, 2010), and is a consequence of metastases from a primary tumour in 85% of cases. Prostate cancer is second only to lung cancer as a cause of metastatic spinal cord compression in men.

Treatment-related side effects experienced by those with advanced prostate cancer include sexual dysfunction, pain, fatigue, urinary tract symptoms, and psychosocial adjustment (Vainio *et al.*, 1996). ASCO recommends that men with metastatic castration-resistant prostate cancer continue hormone therapy to keep androgen levels in the body low, regardless of the other treatments used (Basch *et al.*, 2014). Common long-term side effects associated with Androgen Deprivation Therapy (ADT) include skeletal complications, metabolic and cardiovascular complications, sexual dysfunction, hot flashes, periodontal disease, cognition, and mood disorders. These complications are significant and may be associated with increased overall morbidity, skeletal, metabolic, and cardiovascular complications which have a large impact on morbidity as well as mortality (Shahinian *et al.*, 2006). In one study patients with metastatic prostate cancer reported more severe pain than those with other metastatic cancers (Heim and Oei, 1993). Clark et al. (1997) interviewed men treated for metastatic prostate cancer with castration and found that men's experiences ranged from not being at all worried to being very distressed by bodily changes such as loss of muscle tone, weight gain, breast enlargement, loss of body hair, and hot flushes (Clark *et al.*, 1997). Patients with incurable and life-limiting metastatic conditions are now living longer with serious disease. In contrast to the predictable rapid progression that once typified experiences

of advanced cancer, this phase can now be characterised by an illness trajectory and prognosis that is relatively long and uncertain (Thorne *et al.*, 2013). This thesis will focus on survivorship issues, particularly exercise participation and prescription, in patients with advanced cancer.

1.2.2. Treatment of Advanced Prostate Cancer

Treatment options for men with prostate cancer vary based on staging. For advanced prostate cancer, treatment may include external beam radiotherapy, hormone therapy, such as ADT, and chemotherapy (Figure 5).

External Beam Radiotherapy for the treatment of prostate cancer usually occurs 5 days a week for 4 to 6 consecutive weeks. The goal of radiation therapy is to deliver a curative dose of radiation to the prostate without damaging surrounding tissues such as the bladder, rectum, and bowel. Depending on risk, men may receive radiation to the prostate with or without treatment to the seminal vesicles and with or without androgen deprivation therapy. Complications of external beam radiotherapy include urinary urgency and frequency, dysuria, diarrhoea, erectile dysfunction and urinary incontinence (Jacobs *et al.*, 2014).

The goal of hormone therapy, such as ADT, is to reduce the levels of male hormones called androgens in the body, or to stop them from affecting prostate cancer cells. Androgens stimulate prostate cancer cells to grow. The main androgens in the body are testosterone and dihydrotestosterone (DHT). Most of the androgens are made by the testicles, but the adrenal glands also make a small amount. Lowering androgen levels or stopping them from getting into prostate cancer cells often makes prostate cancers shrink or grow more slowly for a time. Castration may also be accomplished surgically with orchiectomy or chemically with luteinizing hormone-releasing hormone (LHRH) agonists. ADT is accompanied with acute and long-term side effects that may significantly impact quality of life. Acute toxicities include fatigue and hot flashes.As described previously, long-term consequences of ADT include hyperlipidemia, insulin resistance, cardiovascular disease, anaemia, osteoporosis, sexual dysfunction, and cognitive deficits (Loblaw *et al.*, 2007). In one clinical trial, 456 prostate cancer survivors were randomised to receive radiation therapy, or radiation therapy and androgen

deprivation therapy (Pilepich *et al.*, 2001). At follow-up, androgen deprivation was associated with improvement in local control (p=0.016), reduction in distant metastases (p=0.04), disease free survival (p<0.0001), and cause-specific mortality (p=0.05) (Pilepich *et al.*, 2001). Many of the musculoskeletal deficits experienced by those undergoing androgen deprivation therapy, including losses in muscle strength and osteoporosis, may be amendable to exercise therapy/training.

Chemotherapy is also used to treat men with hormone refractory metastatic prostate cancer, with docetaxel-based regimens as standard of care. Adverse effects associated with docetaxel include myelosuppression, hypersensitivity reaction, gastro-intestinal upset, and peripheral neuropathy. For men who have progressed on docetaxel, cabazitaxel may be offered, accompanied by discussion of toxicity risk (Basch *et al.*, 2014). Patients with hormone refractory prostate cancer and those with bone metastases will also be considered for bisphosphonate therapy with zoledronic acid (Perry and Figgitt, 2004), discussed in section 1.4.2. Additional treatment options for patients with hormone refractory metastatic prostate cancer include observation, maximum androgen blockade, withdrawal of antiandrogen and varying specific antiandrogens (e.g. bicalutamide, flutamide, nilutamide). Patients may be eligible for clinical trials or investigational therapies (Chang, 2007). In addition, there are many emerging therapies for this patient group including abiraterone acetate, an oral androgen biosynthesis inhibitor, and denosumab, a monoclonal antibody (Osanto and Van Poppel, 2012). In 2015, the CHAARTED and STAMPEDE-Docetaxel (chemotherapy) studies demonstrated marked survival benefit with the addition of docetaxel to ADT in the metastatic hormone sensitive prostate cancer setting, leading to a change in the standard-of-care for metastatic hormone sensitive prostate cancer. The recent LATITUDE and STAMPEDE-Abiraterone trials showed similar substantial improvement in survival with the addition of abiraterone plus prednisone to ADT in this space (McNamara *et al.*, 2017). Abiraterone used with corticosteroid Prednisone, an oral, synthetic corticosteroid used for suppressing the immune system and inflammation, has the capacity to lower circulating testosterone levels to less than 1 ng/dL (i.e., undetectable) (Small, 2014). Denosumab targets the receptor activator of nuclear factor κB ligand (RANKL), a major contributor to the development and progression of bone metastases.

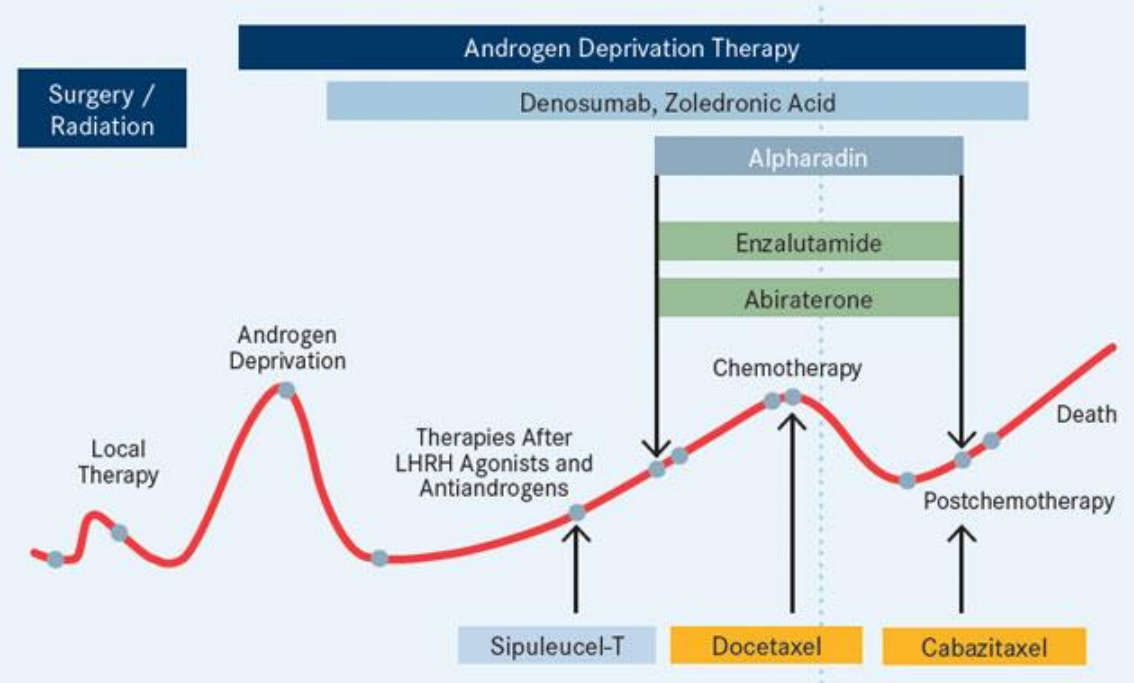


Figure 5 Current Treatment Landscape in Prostate Cancer

Drugs with different mechanisms of action now populate the treatment landscape for prostate cancer. (W.K., 2012).

LHRH: luteinizing hormone-releasing hormone

Over the past 20 years advances in the understanding of tumour biology have led to the development of improved treatment strategies for many cancers. Advances in systemic therapies for cancer have prolonged survival even in those who cannot be cured and many people now live with advanced stages of cancer for longer periods (Weinstein, 1992, Conte and Coleman, 2004). Given that major improvements have been made in our ability to detect, diagnose, and treat prostate cancer in the last two decades, many patients now die with, rather than from prostate cancer. Additionally, many men present with locally advanced or metastatic cancer for whom curative surgery is inappropriate (Jani, 2006). For these men, increases in progression free and overall survival and QOL are the primary management objectives, and new therapies and assisting lifestyle alterations are increasingly needed.

Treatment modalities used specifically in the management of metastatic bone disease will be discussed in section 1.4.2.

1.3. Exercise and Cancer

Exercise is described as physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective (Caspersen *et al.*, 1985). In the last two decades, it has become clear that exercise plays a vital role in cancer prevention and control. Despite the success of recent cancer treatments, as illustrated by improvements in 5-year survival rates, survivors may experience persistent symptoms and side effects of either their cancer, or oncologic treatments (Schmitz *et al.*, 2010). Historically, clinicians advised cancer patients to rest and to avoid activity; however, established research on the benefits of exercise for cancer survivors has challenged this recommendation (Schmitz *et al.*, 2010). Physical activity has emerged as a powerful adjunct to improve the deleterious sequelae experienced during cancer treatment, such as fatigue, muscular weakness and deteriorations in functional capacity (Brown *et al.*, 2012). Exercise may induce positive physiological changes by reducing hormones which promote cell growth and increasing mechanisms which protect the cell. It can also boost the immune system, reduce inflammation and boost antioxidants' pathways (Thomas *et al.*, 2017).

Although there are specific factors associated with cancer treatments that need to be considered with exercise prescription in cancer survivorship, there is consistent evidence that exercise is safe during and after cancer treatment (Schmitz *et al.*, 2010). For adults to gain substantial health benefits, the American College of Sports Medicine suggests at least 150 min/week of moderate-intensity activity or 75 min/week of vigorous-intensity activity (or an equivalent combination). Systematic reviews and meta-analysis have found exercise training–induced improvements in aerobic fitness, muscular strength, QOL, and fatigue can be expected in many cancer types including prostate cancer. Systemic reviews are described as the most reliable source of evidence to guide clinical practice, and are a tool to consume, examine and apply research evidence (Figure 6) (Murad et al. 2016). The American College of Sports Medicine consensus statement on cancer and exercise, concluded that a grade A level of evidence existed for cardiorespiratory benefits from exercise during cancer treatment (Schmitz *et al.*, 2010). In addition, the consensus panel graded the effect of exercise on muscular strength during treatment for breast and prostate cancer survivors as level 'A', with all studies showing marked improvements in muscular strength (Schmitz *et al.*, 2010). Moreover, exercise offers many health benefits to cancer survivors, many of whom remain at increased risk for other chronic diseases including diabetes and heart disease in

survivorship (Schmitz *et al.*, 2010). In addition, a systematic review and pooled analysis of twenty-six studies reported that cancer survivors (mostly with breast, colorectal, and

Figure 6 Evidence-based medicine pyramid.

prostate cancer) who exercised the most had a 37% lower risk of dying from cancer than did survivors who exercised the least (hazard ratio: 0.63; 95% confidence interval: 0.54 to 0.73) (Friedenreich *et al.*, 2016).

Efforts to help survivors avoid inactivity and progress to meeting the exercise recommendations are key to the long-term physical and psychological health of cancer survivors.

1.3.1. Exercise and Prostate Cancer

Exercise is emerging as a successful non-pharmalogical treatment to achieve significant improvements in prostate cancer morbidity and mortality and to work alongside standard treatments such as hormone therapy. A landmark paper in this area reported that men with prostate cancer who exercised vigorously (e.g. cycling, tennis, jogging, swimming) for three or more hours per week had a 61% lower risk of death from prostate cancer compared to men who exercised vigorously for less than one hour per week (Kenfield *et al.*, 2011). Multiple epidemiological studies have suggested that obesity is also associated with increased prostate cancer mortality (Allott *et al.*, 2013) and may represent a key component of the hypothesised mechanisms underpinning the relationship between physical activity and prostate cancer outcome. Patients with prostate cancer, especially those on ADT, may experience many debilitating symptoms from treatment, including changes in body composition. One prospective evaluation following 79 men with non-metastatic prostate cancer from commencement of ADT for

12-months reported significant increases in weight (1.8%, s.e. 0.5%) and fat mass (11.0%, s.e. 1.7%) and decreased lean mass (3.8%, s.e. 0.6%) over the observed period (Smith, 2004). The loss of lean mass and increase in fat mass associated with ADT has major implications for functional independence and the co-morbid disease risk status of patients living with prostate cancer. Exercise may provide a reasonable strategy to counteract the many adverse symptoms of prostate cancer disease and treatments such as ADT as exercise programmes are efficacious in improving body composition, exercise capacity, physical function and QOL in patients with prostate cancer (Bourke *et al.*, 2015). Engaging patients in regular exercise has the potential to improve patient outcomes post-prostate cancer diagnosis and optimise health during treatment (Thune and Smeland, 2000).

1.3.2. Exercise and Advanced Prostate Cancer

Patients with advanced or metastatic prostate cancer live with a considerable disease burden that may have a profound impact on everyday physical function and quality of life (Charalambous and Kouta, 2016). Exercise guidelines for people with cancer, as well people with bone metastases are outlined in Table X.

Table III Exercise Prescription for Patients with Advanced Cancer

Patients Living with Advanced Cancer (No bone metastases)

Exercise Type	Aerobic	Strength	Flexibility
Current Guidelines	At least 150 minutes of moderate aerobic activity OR 75 minutes of vigorous aerobic activity	Strength exercises on two or more days a week that work all the major muscles	Stretch major muscle groups and tendons on days other activities are performed.

Patients Living with Bone Metastases

Exercise Type	Aerobic		Strength			Flexibility
Current Guidelines	At least 150 minutes of moderate aerobic activity OR 75 minutes of vigorous aerobic activity, adapted to Metastases Site:		Strength exercises on two or more days a week that work all the major muscles, adapted to Metastases Site:			Stretch major muscle groups and tendons on days other activities are performed, adapted to Metastases Site:
Metastases Site	WB	NWB	Upper Body	Trunk	Lower Body	Static
Pelvis		√	√	√	√**	√
Axial Skeleton (lumbar)	√		√		√	√***
Axial Skeleton (thoracic/ribs)	√	√	√*		√	√***
Proximal Femur		√	√	√	√**	√
All regions		√	√*		√**	√***

For patients with bone metastases it is advised that exercise guidelines are modified to avoid metastatic sites at risk of pathologic fracture and in accordance with what is realistic for each person (Macmillan.org.uk, 2019). Patients with advanced cancer experience a median of 11 (range 1-27) symptoms of advanced disease (Walsh *et al.*, 2000), some of which may be barriers to engaging in physical activity. However, not all persons with metastatic or advanced cancer are in the palliative or end-of-life phase and many have a great need to maintain good functional capacity. Up to 92% of patients with advanced cancer are interested in completing physical activity programmes (Lowe *et al.*, 2010), however the majority of this patient group are physically inactive (Coleman, 2006). As patients are now living longer with metastatic cancer (Palumbo *et al.*, 2013), the need for physical rehabilitation is increasing, to help counteract the adverse effects of long-term systemic treatments on strength, fatigue and physical functioning. Additionally, exercise is emerging as a synergistic medicine (i.e. increasing the potency or effectiveness of concomitantly applied therapies) and targeted medicine (i.e. exerting its own systemic and localised anticancer effects, independent of other therapies) to underpin delays in disease progression and improvements in survival for advanced cancer patients (Hart *et al.*, 2017). Therefore it is essential to devise and implement exercise interventions suitable for all patients with advanced cancer, including those previously excluded from participation such as patients with bone metastases.

1.3.3. Considerations for Exercise Prescription in Patients with Bone Metastases

A major consideration when prescribing exercise to patients with advanced cancer is the presence of bone metastases. The incidence of bone metastases varies with different primary cancer tumours, ranging from 14% in melanoma to 100% in patients with multiple myeloma. In patients with breast and prostate cancer, the incidence of bone metastases ranges 65-75% (Lipton et al., 2009). As a result of the increased life expectancy of this patient group, the incidences of skeletal metastasis continues to rise, with more than 1.5 million patients worldwide affected by bone metastases alone (Capanna, 2005).

It is essential that physical capacity and independence with activities of daily living in patients with bone metastases are maintained for as long as possible in order to maximise QOL (Santiago-Palma and Payne, 2001). Patients with bone metastases receive long-term systemic treatments which have a significant attritional impact on muscle strength, fatigue and physical functioning. Physical rehabilitation involving exercise and physical activity has a considerable role in counteracting these changes. Patients with bone metastases respond well to rehabilitative treatment (Bunting and Shea, 2001) with evidence from systematic reviews of exercise interventions reporting improvements in functional capacity, lower fatigue levels and increased QOL (Beaton et al., 2009, Salakari et al., 2015).

Despite the known benefits of physical activity for patients living with cancer, exercise prescription in patients with metastatic disease is challenging. Exercise is often perceived as a contraindication in the presence of bone metastases due to concerns about aggravating skeletal related events (SREs) (Porock et al., 2000, Cormie et al., 2013, Nadler et al. 2017). In Chapter 5 of this thesis the views of clinicians and physiotherapists will be explored to provide a greater understanding of the concerns surrounding exercise prescription to patients with advanced disease. The consequences of SREs, such as pathological fractures and extradural spinal cord compression, include severe pain, increased health care costs, reduced QOL and increased mortality (Saad, 2013). Amongst patients however, interest in physical activity is high. As mentioned previously, one cross-sectional study of 50 patients living with a high burden of metastatic bone disease reported that 92% of patients were interested in completing exercise programmes and felt able to do so (Lowe et al., 2010). Despite this only 29% of patients with bone metastases meet the current aerobic exercise guidelines for cancer survivors (Zopf et al., 2017), suggesting that despite a keen interest, physical activity levels in this population are suboptimal.

1.4. Narrative Literature Review

This thesis specifically examines exercise prescription in patients with advanced prostate cancer. The ExPeCT randomised controlled trial will recruit men with prostate cancer to a six month exercise intervention (Chapter 6). As a large number of patients advanced prostate cancer present with bone metastases, the prescription of exercise to this patient group requires careful consideration.

The following section provides an overview of factors for consideration with exercise prescription in metastatic bone disease. The evidence from trials of exercise prescription in this population will be reviewed to address the challenges with exercise prescription in this population. The manuscript to accompany this narrative review is currently in press in the Physical Medicine and Rehabilitation Journal. The review will examine (i) the physical sequelae of bone metastases to determine the non-lethal long-term adverse effects occurring in patients living with bone metastases (ii) factors to consider with exercise prescription, given the negative effects of treatment and the associated co-morbidities, and (iii) a comprehensive literature review of structured exercise training in patients with metastatic bone disease to synthesise the evidence in this area (Figure 7).

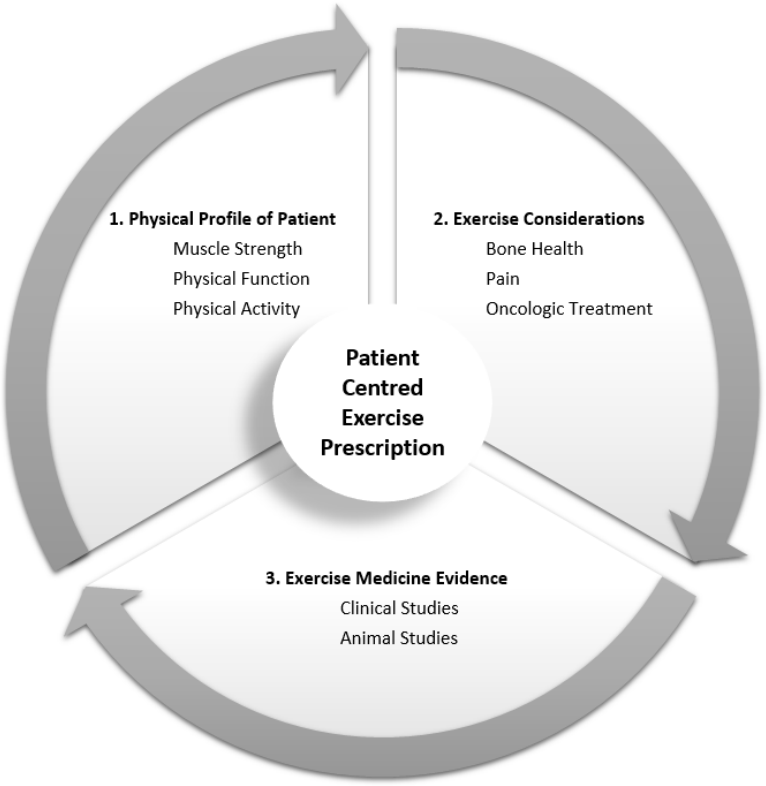


Figure 7 Exercise Prescription Considerations for patients with Metastatic Bone Disease

1.4.1. Section One: The Physical Profile of the Patient

Metastatic cancer and its associated treatment have a considerable attritional impact on multiple components of physical performance including muscle strength, physical function and physical activity. The following section provides an overview of the unique and multifaceted clinical profile of this patient cohort.

1.4.1.1. Muscle Strength

Skeletal muscle loss and muscle weakness are a well-described sequela of early-stage cancers (Galvao *et al.*, 2009, Klassen *et al.*, 2017). While less is known about skeletal muscle impairment in metastatic bone disease, it is associated with treatment toxicity and time-to-tumour progression (Prado *et al.*, 2009), and therefore it is of considerable clinical importance. A small number of cohort studies have reported suboptimal muscle strength in patients with metastatic bone disease (Massy-Westropp *et al.*, 2011, Oldervoll *et al.*, 2011, Trosclair *et al.*, 2011). In one example in metastatic breast cancer (n=71) both relative and adjusted grip strength (26.6 (6.0) vs 30.2 (6.4)kg (p=0.001) and 0.38 (0.09) vs 0.46 (0.11) $kg.kg^{-1}$ ($p<0.001$) respectively), and leg strength ((53.5 (23.7) vs. 76.0 (27.4) kg ($P<0.001$) and 0.76 (0.31) vs 1.15 (0.45) $kg.kg^{-1}$($P<0.001$)) were significantly lower than matched healthy controls (Yee *et al.*, 2014). Hand grip strength is negatively associated with physical frailty and low scores are predictive of disability in older people (Dudzińska-Griszek *et al.*, 2017). The absolute values and precision of grip strength measurements can be influenced by aspects such as allowance for hand size and dominance, posture, joint position, effort and encouragement, frequency of testing and time of day, and training of the assessor (Roberts et al. 2011). Despite this, hand-held dynamometry can be a reliable assessment technique when practiced by a single experienced tester (Bohannon 1986).

Additionally, measures of lower limb muscle function, such as 30 second sit-to-stand (STS) test scores, are impaired in metastatic cohorts, with patients completing approximately half the number of STS repetitions (11.5 (4)) in comparison to matched controls (22 (7)) (Oldervoll *et al.*, 2011, Millor *et al.*, 2013). In patients with spinal metastases, pre-intervention data from an exercise study reported baseline STS repetitions as low as 5.1 (1.4) (intervention) and 4.6 (2.0) (control), however this outcome was amenable to rehabilitation, with the intervention arm increasing to 9.0 (2.6) repetitions following 3-months of isometric spinal strengthening (Rief *et al.*, 2014). Of concern, in older healthy cohorts (>60 years old), 30s-STS <15 repetitions is predictive of falls risk and fracture risk and therefore the consequences of the low STS repetition values observed in patients with metastatic bone disease may be considerable (Jones *et al.*, 1999).

1.4.1.2. Physical Function

Physical function involves the performance and co-ordination of various physiological systems, all of which may be impaired as a result of cancer treatment (Garber *et al.*, 2010, Brown *et al.*, 2015). Physical function may be measured in a number of different ways, including both subjective and objective physical performance measures, which show comparable levels of validity, sensitivity and responsiveness (Latham *et al.*, 2008, Reiman and Manske, 2011).

Subjective measures of physical function are commonly used for patients with metastatic bone disease, such as the physician-completed Musculoskeletal Tumour Society Score (MTSS) and the patient completed Patient-Reported Outcome Measurement Information Systems (PROMIS) Physical Function Cancer questionnaire, a superior measure of physical function in patients with lower extremity bone metastases due to its validity, brevity and reliability over a wide range of ability levels (Janssen *et al.*, 2016). Patients diagnosed with cancer report a mean PROMIS Physical Function (short form) score of 44.9, one half standard deviation lower than the overall U.S. population mean, while patients with lower extremity bone metastases report lower median scores of 36 (IQR 31–43) (Jensen *et al.*, 2015, Janssen *et al.*, 2016).

Measurement tools that incorporate objective measures of physical function, such as the short physical performance battery and fast gait speed, are predictive of premature mortality in all cancer survivors (Brown *et al.*, 2015). In metastatic non-small cell lung cancer, one prospective study (n=118) reported that six-minute walk distance (6MWD) was independently predictive of survival, with patients achieving 6MWD <358.5 having greater chance of all-cause mortality compared to 6MWD 358.5-450 (adjusted hazard ratio (HR) 0.61 (95% CI, 0.34-1.07) and 6MWD >450 0.48 (95% CI, 0.24-0.93) (Jones *et al.*, 2012).

1.4.1.3. Physical Activity

Current evidence suggests many health benefits from physical activity during and post-cancer treatments (Speck *et al.*, 2010). Studies in patients with metastatic disease however, have shown that this patient group are at significant risk of low physical activity levels. In a cross-sectional study of 55 patients living with metastatic bone disease using

subjective methods of physical activity assessment, 71% of participants were insufficiently active and did not meet the current aerobic exercise guidelines for cancer survivors (Zopf *et al.*, 2017). When measured using objective methods, physical activity levels are considerably lower. In a cross-sectional analysis of 71 patients with metastatic breast cancer (n=19 bone-only metastases) physical activity levels were significantly lower than healthy counterparts, achieving only 56% of the steps completed by controls each day (5,434 (3,174) vs 9,635 (3,327) of steps/day ($p<0.001$)) (Yee *et al.*, 2014). Objective PA levels in patients receiving radiotherapy for bone pain are comparable to physical activity levels in patients receiving chemotherapy (Ferriolli *et al.*, 2012). As objective physical activity scores correlate significantly with QOL of patients with cancer, there is a need for strategies to increase physical activity levels in metastatic patients (Ferriolli *et al.*, 2012).

1.4.2. Section Two: Exercise Considerations for Patients with Metastatic Bone Disease

As described in section 1.3 all cancer survivors, including patients living with bone metastases, are advised to engage in 150min of weekly moderate-intensity aerobic exercise and to include strength and flexibility training in their programme (Schmitz *et al.*, 2010). For patients with bone metastases however, achieving these guidelines may prove challenging. Even when encouraging patients to be as physically active as their abilities and conditions allow, exercise prescription is complicated by several factors associated with bone lesions including compromised bone health, risk of pathological fracture and increased pain levels. Considerations for exercise prescription in the presence of these complications is considered below.

1.4.2.1. Bone Health

Osteoporosis

Osteoporosis and osteopenia are a common sequela for patients with bone metastases. This is due to the direct effects of cancer cells on the skeleton and to deleterious effects of cancer-specific therapies on bone cells (Drake, 2013). In a case controlled analysis of 174 hormone naive men with advanced prostate cancer, 42% were osteoporotic and 37% were osteopenic at diagnosis compared to a 27% incidence of osteoporosis amongst peer-matched controls (p=0.02) (Hussain *et al.*, 2003). Additionally, steroid use, often used in advanced cancer for disease control and symptom management, is a strong independent risk factor for fractures (Wooldridge *et al.*, 2001, Caro *et al.*, 2004). Osteoporosis often arises as a side-effect of cancer therapies such as ADT for prostate cancer, aromatase inhibition for breast cancer, or chemotherapy-induced ovarian failure (Winters-Stone *et al.*, 2014). ADT, the most commonly used therapeutic strategy for men with advanced prostate cancer, increases bone turnover and decreases bone mineral density (BMD), leading to a 20% - 45% increase in relative fracture risk (Mohler *et al.*, 2010). Additionally, a large randomised study examining the effects of hormone treatment the bone health in patients with metastatic breast cancer found that, relative to baseline, endocrine therapy independently resulted in BMD declines at the lumbar spine (−11.3%) and hip (−7.3%) over 36 months (Drake, 2013).

Osteoporosis management involves a multimodal approach comprising pharmacological and conservative interventions. Conservatively, education about potentially fracture-risk

activities such as heavy lifting or high-impact activities, and the introduction of individualised exercise programmes for muscle strengthening and falls prevention are recommended (Kanis *et al.*, 1997). A large retrospective study has shown that abandoning general corset use in patients with spinal metastases does not increase rates of pathological fracture in patients with spinal bone metastases after radiotherapy (Rief *et al.*, 2015). Functional loading activities such as walking exert a positive influence on bone mass (Cosman *et al.*, 2014). Changes in bone mass occur more rapidly with unloading than with increased loading (Kohrt *et al.*, 2004). Therefore, patients with bone metastases experiencing osteopenia and osteoporosis should be encouraged to, at the very least, maintain PA levels for as long as possible in order to preserve bone mass.

Pathological Fracture

A fracture that develops in an area of bone pathology, such as a secondary metastases, is termed a pathologic fracture, the consequences of which include severe bone pain, mobility limitations and the possibility of surgery and hospitalisation (Sonmez *et al.*, 2008). The incidence of pathological fracture ranges from 43% in patients with multiple myeloma to 17% in patients with metastatic lung cancer (Saad *et al.*, 2007). Risk factors for pathological fracture include the size of the lesion and higher pain scores, however little is known about the influence of PA on fracture rates. In one prospective study of 54 patients with bone metastases receiving inpatient rehabilitation, 16 fractures occurred in 12 patients, with only one fracture associated with rehabilitation. Patients in the fracture group were significantly more likely to be female, younger, have a larger number of metastatic sites and a previous occurrence of pathologic fracture (Bunting *et al.*, 1985). Additionally, lytic metastases (those that break down bone), common in myeloma or renal cell carcinoma, were more likely to develop into fractures when compared with osteoblastic metastases (those that stimulate bone growth), common in prostate cancer. If patients are referred to rehabilitation following a pathological fracture, hypercalcemia and administration of parenteral narcotics suggest a poor rehabilitation outcome. Despite this, patients with pathologic fractures secondary to metastatic disease are considered excellent candidates for intensive rehabilitation programs (Bunting *et al.*, 1992).

In consideration of the multifaceted nature of fracture risk, algorithms such as Mirel's Classification Scoring system can provide a useful measure of fracture risk. Mirel's Classification is physician led, and is one of the most common methods of assessing risk in clinical practice, although the use of CT based methods with increased specificity is increasing (Benca et al. 2016). This system encompasses multiple details including the site of metastases, patient reported pain level, x-ray appearance and size of the

lesion (Figure 8). A resulting score >8 suggests prophylactic fixation is required. The system has good sensitivity but relatively poor specificity (Jawad and Scully, 2010).

Score	1	2	3
Site	Upper Limb	Lower Limb	Trochanteric
Pain	Mild	Moderate	Functional
X-Ray appearance	Blastic	Mixed	Lytic
Size of Lesion	<1/3 cortex	1/3-2/3 cortex	>2/3 cortex

Figure 8 Mirel's scoring system for pathological fracture prediction

While not currently used widely in exercise oncology, assessing patients for risk of fracture using tools such as Mirel's criteria could form a useful basis for exercise prescription. The scoring system has potential be used as a decision tool for selecting patients suitable for exercise interventions and also be used as an aid the selection of suitable exercises for completion. Just one study in patients with multiple myeloma, a cohort similar to metastatic bone disease, has used Mirel's Classification to screen for fracture risk and exercise suitability. In this analysis there were 13 (21.6%) screen failures from a total of 75 eligible participants due to fracture risk, typically large lytic lesions of the long bones or extensive lytic disease in the pelvis. Those not at risk were recommended for exercise, while others deemed at risk underwent cross-sectional imaging with CT or MRI and were referred for surgery and/or radiotherapy before embarking on the exercise programme (Smith *et al.*, 2015).

Other fracture screening tools such as the WHO screening tool (FRAX) (Adler, 2011) may also be useful. The FRAX calculator, (www.shef.ac.uk/FRAX/), identifies 10-year fracture risk. The FRAX accounts for hormone therapy by classifying it as secondary osteoporosis and is considered superior to using measures of bone mineral density alone to determine fracture risk (Saylor *et al.*, 2010). A number of recent studies have investigated the value of CT based-Finite Element three-dimensional modelling and CT-based structural rigidity analysis in predicting fractures. Both methods may considerably advance the accuracy of pathological femur fracture prediction (Goodheart *et al.*, 2015, Damron *et al.*, 2016), however in clinical practice where this level of radiological analysis is not available Mirel's classification can provide an extremely meaningful and cost-effective measure of fracture risk.

Pain

Bone pain is usually the earliest and most common symptom of bone metastases (Sabino and Mantyh, 2005). Up to 83% of patients with metastatic bone disease complain of cancer induced bone pain, with wide variations in pattern and severity (Laird *et al.*, 2011). Incident or breakthrough pain (BTP), defined as an abrupt, short-lived, and intense flare of pain in the setting of chronic pain, may be a significant factor affecting exercise prescription (Ghosh and Berger, 2014). The Brief Pain Inventory, which evaluates pain severity and the resulting functional interference, is a valid and reliable tool for pain measurement in patients with bone metastases (Chow *et al.*, 2010, Wu *et al.*, 2010). Using this tool, patients with bone metastases (n=258) report substantial pain-related interference in activity; despite the classification of pain levels as mild or moderate (Wu *et al.*, 2010). Therapists should be aware that unidimensional measures of pain (e.g. Numerical rating scales) do not always correlate with physical function. Measures such as the BPI ensure both pain severity and pain interference on function are measured. Relatively mild pain intensity scores (~2 points) could conceal clinically important functional impairments in patients with lower body metastases, and attention to activity function is critical during assessment.

Pain associated with functional activity is associated with higher risk of pathological fracture, and hence is an integral component of risk prediction models such as Mirel's classification. In one study of 66 consecutive patients with 100 metastases in long bones, only six out of 57 bone lesions that were classified by patients as mildly or moderately painful later fractured, however all lesions in which pain was aggravated by function subsequently fractured (Fidler, 1981). Therefore, while many of this patient group will receive regular analgesia for bone pain, those experiencing BTP, particularly associated with functional activity, should be investigated fully prior to commencing exercise programmes. Exercise studies in patients with bone metastases have monitored pain levels closely, modifying the intervention if pain increases (Cormie *et al.*, 2014). If pain persists, orthopaedic opinion may be required prior to the continuation of exercise and in cases of severe pain, before the patient can resume activities of daily living. Pain is also a predictor of metastatic spinal cord compression (MSCC) (Figure 9), present in 83 -95% of patients at the time of diagnosis (NICE, 2008).

Current methods of predicting fracture risk do not consider the absolute amount of weight that is placed on the bone, however, it has been proposed that greater patient body weight leads to greater fracture risk (Bunting and Shea, 2001). There is uncertainty around the level of weight bearing a patient with bone metastases can be permitted. In

one study of 38 patients with 78 long bone lesions, there were no differences in the rate of pathological fracture between patients completing weight bearing versus non-weight bearing activity, indicating patients should be encouraged to engage in pain-free weight bearing activity (Mirels, 1989, Riccio *et al.*, 2007). Conversely, pain with weight-bearing activities can indicate pathologic fracture, particularly in the lower extremities, and therefore weight bearing activities should be avoided in the presence of pain. This further emphasises the need to monitor pain throughout exercise sessions and modify treatments accordingly.

Clinical vigilance must be exercised with rehabilitation and exercise prescription to these patients. Any worsening of pain and neurological symptoms should be recorded, reported and medical advice sought. If pain or neurological symptoms worsen during rehabilitation, the activity should be stopped, and the patient returned to a spinal protective position where these changes reverse.

Medical Emergency: Metastatic Spinal Cord Compression

- Pain, usually severe local back pain, at the level of the lesion, which progressively increases in intensity, is usually the first symptom of MSCC (NICE, 2008).
- The Gain Guidelines for the Rehabilitation of Patients with Metastatic Spinal Cord Compression suggest that stability of the spine and the level of mobility allowed should be agreed by the multi-disciplinary team (GAIN, 2014).
- Clinical vigilance must be exercised with rehabilitation and exercise prescription. Any worsening of pain and neurological symptoms should be recorded, reported and medical advice sought.
- If pain or neurological symptoms worsen during rehabilitation, the activity should be stopped, and the patient returned to a spinal protective position where these changes reverse.

Figure 9 Metastatic Spinal Cord Compression

1.4.2.2. Oncologic Treatment

The main goal of treatment for bone metastases is to reduce the incidence of skeletal related events (SREs) and improve QoL and mobility. In addition to standard anti-cancer therapies such as chemotherapy and hormone therapy, discussed in section 1.2.2.

above, modern treatment of metastatic bone disease includes analgesics, radiation therapy, surgery and bisphosphonate drugs (Yang and Du, 2015). The following section will discuss each of these treatments, as well as describing the impact each will have on patients' physical function and performance. All treatments will alter rehabilitative goals and patient suitability for particular interventions and therefore awareness of each of the following treatments will guide therapists to tailor exercise prescription.

Analgesics

Effective analgesia is fundamental to a patient's ability to participate in exercise. Adequate pain relief significantly increases mobility and general activity in patients with bone metastases (Petcu *et al.*, 2002). The pharmacologic approach to the treatment or palliation of painful osseous metastases follows the World Health Organization (WHO) analgesic stepladder. This "triple opioid therapy approach" involves 1) Controlled release opioids (to control background constant pain), 2) Immediate release opioids (to control gradual onset breakthrough pain), and 3) Rapid-onset opioids (to control sudden increases in pain). Analgesic agents may include: non-opioid analgesics (e.g. non-steroidal anti-inflammatory drugs), adjuvants (e.g. antidepressants, muscle relaxants), and opioids/opioid-like analgesic agents (Smith and Mohsin, 2013). It is particularly difficult to achieve pain control when bone metastases cause pain on movement (Petcu *et al.*, 2002). Often nonsteroidal anti-inflammatory drugs and opioid analgesics are ineffective and further interventions, such as those detailed below, are required.

Radiation Therapy

Palliative radiotherapy can successfully relieve symptoms of advanced cancer, with the most common indication for its use being localised, uncomplicated painful bone metastases (Lutz *et al.*, 2010). Large multi-institutional randomised trials have demonstrated that 80% of patients receiving radiotherapy for osseous metastases will experience complete to partial pain relief, typically within 10-14 days of the initiation therapy (Tong *et al.*, 1982). Pain and pain interference have been shown to cluster with nausea when patients are receiving radiation therapy (Ganesh, 2018). Pain reduction, measured with the BPI, is associated with positive changes in physical function (Wu *et al.*, 2006). In contrast, neither location of bone metastases nor radiotherapy dose predict pain response or functional interference following radiation treatment (Zeng *et al.*, 2012). Studies prescribing exercise for patients receiving palliative radiation treatment report no adverse events (Oldervoll *et al.*, 2011, Litterini *et al.*, 2013, Rief *et al.*, 2014a). The only documented precaution specific to exercise prescription in patients following

radiotherapy is a severe tissue reactions such as dryness, itching, blistering, or peeling, leading to increased risk of infection (Stefani *et al.*, 2017).

Surgical Intervention

Surgical interventions for metastatic bone lesions are completed to relieve pain or neurological symptoms, stabilise fractures, restore function, enable ambulation and overall increase patient QOL (Zore *et al.*, 2009). A pathologic fracture exposes patients to extreme pain, urgent hospitalisation, and the risk of emergency surgery with compromised outcome. Thus, predicting impending fracture and prophylactic fixation in an elective setting are critical to avoid debilitating complications.

In patients who experience pathological fracture, surgical intervention can lead to significant improvements in physical function and activity levels (Zore *et al.*, 2009). For example, in a study of 67 patients who underwent surgery for long bone fractures caused by metastatic tumours, significant improvements in physical function were reported in measures of activities of daily living such as washing and dressing (Zore *et al.*, 2009). For patients with malignant spinal tumours, percutaneous vertebroplasty and kyphosplasty are effective minimally invasive procedures which provide analgesia and spinal stabilisation that restore or preserve ambulation (Gokaslan *et al.*, 1998, Saliou *et al.*, 2010, Qian *et al.*, 2011). Weight bearing status may vary post-operatively depending on bone quality and types of fracture pattern as well as surgical procedure, and therefore a collaborative approach to post-operative mobilisation involving the surgical and physiotherapy team is advised (Carlin *et al.*, 2016).

Bone modifying agents

Bone modifying agents have some analgesic effect and reduce the risk of SREs, while reducing the need for palliative radiotherapy and surgery (Hortobagyi, 2011, Serpa Neto *et al.*, 2012). Two classes of agents used are the bisphosphonates (pamidronate, zoledronic acid (ZA), clodronate and ibandronate) and the RANK ligand inhibitor, denosumab (NCCC, 2008, Narayanan, 2013, Hayes, 2016). Bisphosphonates are associated with acute-phase reactions in approximately 15%-20% of patients (primarily after the first one or two infusions), which are characterised by mild to moderate flu-like symptoms such as low-grade fever, fatigue, arthralgia or myalgia, increased bone pain and nausea (Zojer *et al.*, 1999). This can begin days or months after starting treatment. Patients may require additional analgesia and adaptions to exercise programmes until symptoms improve (Coleman, 2005). Intravenous bisphosphonates are the treatment

of choice for the initial management of hypercalcaemia (Figure 10) (Ralston, 1992). The effect of exercise was compared to the effects of bisphosphonates (ZA) in one randomised controlled trial. At 12 months, spine, total hip, and total body BMD increased in the ZA group by 1.6%, 0.8%, and 0.8%, respectively, however BMD decreased in the PA group by 6.0%, 3.4%, and 3.3%, respectively (P values < 0.0001 for all group comparisons). ZA protected patients with breast cancer against bone loss during initial treatment, whereas home-based physical activity interventions were less effective in preventing bone loss (Swenson *et al.*, 2009).

Medical Emergency: Hypercalcemia

- Hypercalcaemia is an abnormally large amount of calcium in the blood which affects up to 10% of patients with advanced cancers (Mirrakhimov, 2015).
- The clinical features of hypercalcemia include neurological changes, cognitive changes, gastrointestinal, renal and cardiovascular symptoms (Mirrakhimov, 2015).
- Asymptomatic or mildly symptomatic individuals with hypercalcemia may not require immediate therapy. However, hypercalcemia with malignancy usually presents with markedly elevated calcium levels (>3.5 mol/L) and therefore is usually severely symptomatic and is considered on oncological emergency (Mirrakhimov, 2015).

Figure 10 Hypercalcemia

1.4.3. Section Three: Exercise Medicine Evidence

Given the potential for exercise to enhance function, ameliorate the side-effects of treatment or act as an adjunct to modern anti-cancer treatments, the purpose of this comprehensive literature review was to synthesise the available evidence concerning exercise programmes involving patients with metastatic bone disease.

1.4.3.1. Methods

Papers were identified through a search of the following databases: CINHAL, EMBASE, Medline, PubMed, SCOPUS and Web of Science on 23rd March 2017. The search terms used included combinations of physical activity or exercise and key words related to

bone metastases, including 'bone metastases', 'spine metastasis', ‘advanced cancer’, ‘advanced neoplasm’, ‘bone neoplasms’, ‘spinal neoplasms’, ‘pelvic neoplasms’, ‘spine metastases’, ‘spontaneous fracture’, ‘pathologic fracture’, ‘bone pain’ and ‘fragile bone’. In addition, studies retrieved from journal publication reference lists, and any other published studies known to the authors were also included. The search included the literature up to April 2017. No limits were applied to the searches.

Studies which met the following criteria were included:

- Studies involving adults living with bone metastatic disease,
- Included Participants with metastases resulting from solid primary tumours,
- The intervention which included a supervised exercise programme

Studies involving paediatric patients were not included. Where it was unclear if patients with bone metastases were included or were eligible for inclusion, the authors of the paper were contacted for clarification. The results of the literature search were screened by two authors for inclusion in the current review. A flow diagram of the literature search and selection is presented in Figure 11. Details relating to exercise programmes prescribed, adverse events and outcomes related to physical activity, physical function and QOL were extracted from studies.

Given the complexity of biological systems, the use of animal models has provided a significant understanding of the various adaptive mechanisms undergoing acute and chronic physical exercise (Angelis *et al.*, 2017). Studies examining the effect of exercise training in animal models with metastatic bone disease were also included.

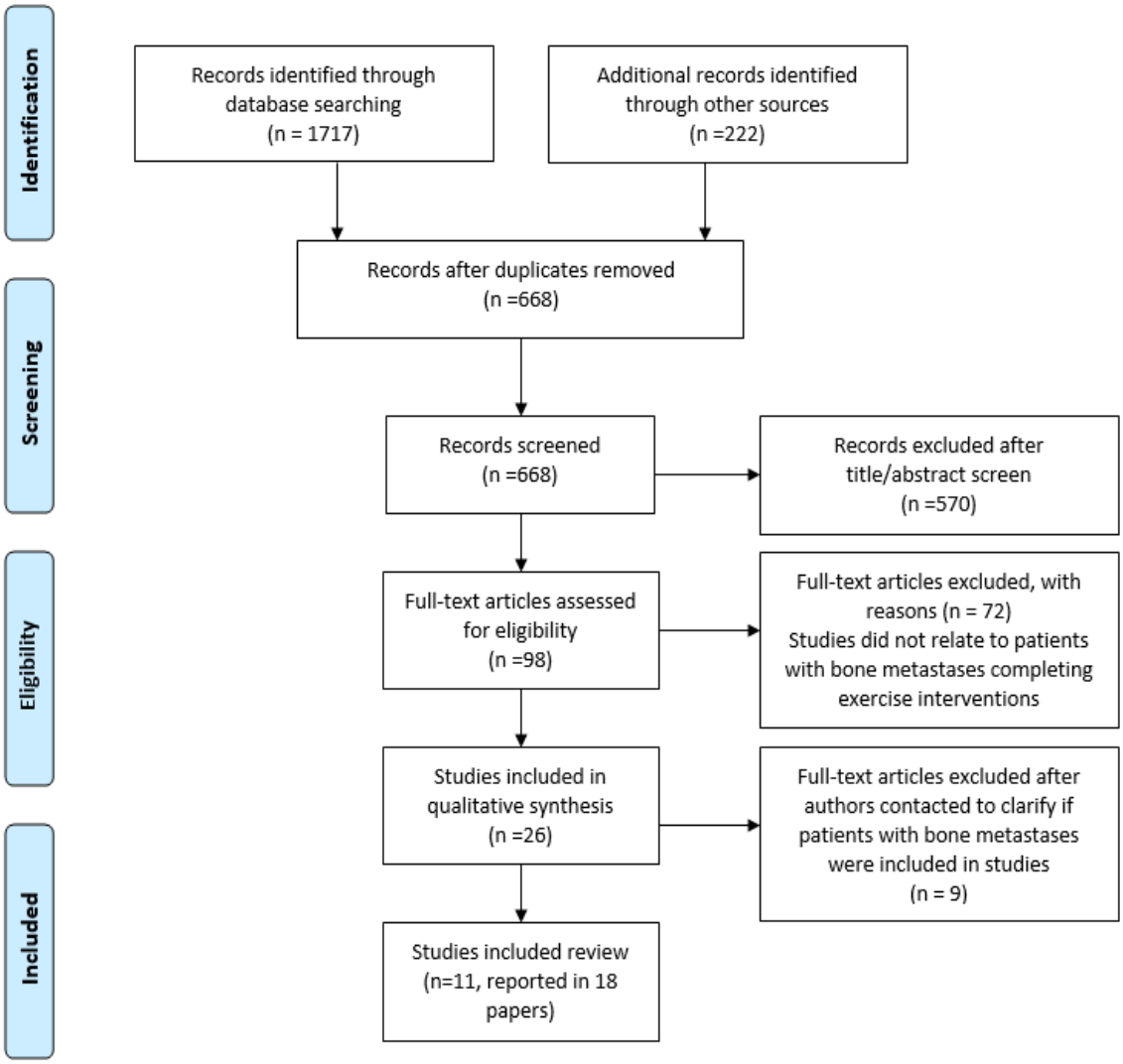


Figure 11 Comprehensive Literature Search Flowchart

1.4.3.2. Results of Comprehensive Literature Review

Eleven studies, described in 18 papers, relating to exercise prescription in patients with bone metastases were considered eligible for inclusion; seven randomised controlled trials, three single-arm studies and one multi-arm interventional study. Aerobic and/or resistance exercise training was prescribed by all studies. Five studies examined aerobic and resistance training as a multimodal intervention and one study compared an aerobic training intervention to a resistance training intervention. In addition, three studies prescribed resistance training only, while two studies prescribed aerobic training only.

Animal studies included for review prescribed exercise or lower limb training interventions.

All studies reviewed included patients with metastatic bone disease. In six studies, participants had a diagnosis of primary prostate cancer, while four studies included participants who had a mixture of primary cancer diagnoses. One study included only patients with metastatic breast cancer. In total, studies involved 593 patients with metastatic disease, of which 347 were prescribed exercise. The remaining 246 patients served as control subjects. Participant age ranged from 49 to 73.1 years and BMI ranged from 26.6 to 29.3kg/m^2.

1.4.3.3. Studies Involving Aerobic Exercise

Two studies reviewed prescribed aerobic exercise as a uni-modal intervention.

The first prescribed a 12-week, RCT of football training programme for men undergoing ADT for advanced or locally advanced prostate cancer (n=57), 11 of whom had metastatic bone disease (Ligibel et al., 2016). The football training group (n=29) practiced 2–3 times per week for 45–60 minutes while a standard care control group (n=28) were instructed to maintain their baseline activity levels. Post-intervention, the football group demonstrated favourable between group differences in total body bone mineral content [26.4 (95% Confidence Interval (CI): 5.8–46.9g; p=0.013], leg bone mineral content [13.8 (95% CI: 7.0–20.5g; p<0.001)] and markers of bone formation. Knee extensor strength (1RM) demonstrated a mean group difference of 6.7 kg (95% CI 2.8–10.7; P < 0.001), in favour of the football group. There were no changes in aerobic fitness or body fat percentage (Uth *et al.,* 2016b). In relation to adverse events, two fibular fractures were reported in the football arm however they did not involve patients with bone metastases and were considered as accidental and unrelated to metastatic disease (Uth *et al.,* 2016a).

The second intervention prescribed a 16-week programme of moderate intensity exercise in patients with metastatic breast cancer (Ligibel et al., 2016). Participants were randomised to either an intervention arm (n=48) or a waiting-list control group (n=53). The intervention group completed individual exercise sessions at a local gym, with a target weekly exercise goal of 150 minutes moderate intensity exercise. In contrast to the prostate study described above, this training programme did not result in improvements in weekly exercise, physical functioning or aerobic fitness.

1.4.3.4. Studies Involving Resistance Exercise

Three studies reviewed prescribed resistance exercise as a uni-modal intervention. Cormie et al. examined the feasibility of resistance exercise interventions for patients with metastatic bone disease in two papers, a RCT and single-group (uncontrolled) longitudinal study (Cormie *et al.*, 2013, Cormie *et al.*, 2014). In the first, twenty men with established bone metastases secondary to prostate cancer were randomly assigned to a 12-week resistance exercise programme (n=10) or usual care group (n=10). Participants had significant disease load with 65% of participants presenting with two or more regions affected by bone metastases. Exercise was prescribed to avoid loading bones and minimise sheer forces on areas of the body with metastatic lesions (Figure 12).

Metastases Site	Exercise mode					
	Resistance			Aerobic		Flexibility
	Upper	Trunk	Lower	WB	NWB	Static
Pelvis	√	√	√**		√	√
Axial Skeleton (lumbar)	√		√		√	√***
Axial Skeleton (thoracic/ribs)	√*		√	√	√	√***
Proximal Femur	√	√	√**		√	√
All regions	√*		√**		√	√***

Figure 12 Guide for prescribing exercise for patients with bone metastases

√ = Target exercise region; * = exclusion of shoulder flexion/extension/abduction/adduction – inclusion of elbow flexion/extension; ** = exclusion of hip extension/flexion – inclusion of knee extension/flexion; WB weight bearing (e.g. walking); NWB non weight bearing (e.g. cycling); *** = exclusion of spine flexion/extension/rotation (Galvao et al. 2017)

Exercise prescribed using this approach was well tolerated and did not increase the incidence of skeletal complications. At three months, muscle strength, measured by leg extension 1RM increased significantly with a mean adjusted group difference of 7.6 kg ($p=0.016$). Submaximal exercise capacity and ambulation also improved, with a mean group difference of -13.7 seconds in a 400m walk ($p=0.010$) and a mean group difference of -0.55s in a 6m walk ($p<0.001$). Low intensity exercise participation, measured with

accelerometers, increased from 341.7 ±143.3 min/week to 356.7 ±112.6 min/week in the intervention group (p=0.003). No significant between-group differences were observed for fatigue, QOL or psychological distress. In the second study by this author (n=20), a 3-month resistance exercise intervention, followed by a 6-month follow up assessment, found that gains in ambulation (p=0.046), increases in weekly minutes of resistance exercise (p=0.003) and whole body lean mass (p=0.039) were maintained at follow-up in the intervention arm (Cormie *et al.*, 2014).

Using a different approach, Rief et. al. (2014) examined the effect of isometric resistance exercise training of the paravertebral muscles compared to breathing exercises in a group of patients with spinal bone metastases receiving radiotherapy (n=60). The intervention involved 30 minutes of exercises which were performed on each day of radiotherapy treatment over a 2-week period, and continued three times a week for 6 months (Rief *et al.*, 2014). Pain scores reduced from 48/100 at baseline to 16/100 post-intervention in the intervention arm compared to no change (51/100 to 50/100) in the control group ($p < .001$) (Rief *et al.*, 2014). No differences in fracture rate was found between groups after either 3 (p=0.59) or 6 months (p=0.60). Furthermore, survival analysis detected no difference in overall survival or progression-free survival between the two arms of the trial (Rief *et al.*, 2016). Additionally, pyridinoline and beta-isomer of carboxy-terminal telopeptide of type I collagen, biomarkers of bone turnover, decreased significantly in the resistance arm in comparison to the control group. These biomarkers may be used as a complementary tool for predicting local response to treatment, and for avoiding SRE (Rief *et al.*, 2016).

1.4.3.5. Studies Comparing Aerobic to Resistance Exercise

One randomised trial assigned 66 patients with metastatic cancer, including patients with bone metastases, to a programme of either individualised resistance (n=34) or aerobic exercise (n=32) (Litterini *et al.*, 2013). At 10 weeks there were significant improvements in Short Physical Performance Battery (SPPB) total score (P<.001), gait speed (p=.001), and fatigue (p=.05) in both groups. Analyses of SPPB scores found that regardless of group, gait (p=0.002) and chair stand (p<0.001) sub scores improved significantly over time, however balance sub scores did not change in either group. Neither resistance nor aerobic training aggravated fatigue or pain. There did not appear to be a substantial differential effect of one mode of exercise compared with the other.

1.4.3.6. Studies Prescribing both Aerobic and Resistance Exercise

Five studies examined the effects of multimodal interventions prescribing both aerobic and resistance programmes to patients with metastatic bone disease.

A recent randomised controlled trial examined the effects of a multi-modal exercise programme of resistance, aerobic and flexibility exercise on physical function in patients (n=57) with metastatic prostate cancer. The exercise intervention, undertaken three times per week, resulted in self-reported improvements in physical function (p=0.028) and objectively measured lower body muscle strength (p =0.033), with no skeletal complications or increased bone pain (Galvao *et al.*, 2017). The largest programme reviewed (n=231), randomised patients to an 8-week aerobic and resistance programme or to a usual care control group. The supervised exercise intervention lasted 60 minutes and included a warm up, circuit training with six stations, stretching and five minutes of relaxation. Clinically and statistically significant between-group effects were found in shuttle walk test scores (estimated mean difference of 60m (95% CI, 16.0 –103.4 m; *p*= .008) and hand grip strength scores (estimated mean difference of 2.0kg (95% CI 0.4–3.5) in favour of the exercise group post intervention. However, no significant between group effects in the primary outcome, fatigue were reported (Oldervoll *et al.*, 2011).

In contrast, a single-arm feasibility study of a lifestyle intervention for sedentary men with advanced cancer receiving ADT found significant within-group improvements in FACT-F scores (p<0.001) at 12 weeks. Participants completed 30 minutes of supervised resistance and aerobic exercise twice weekly for the initial six weeks and then once weekly for the following six weeks. Positive changes were maintained at a six month follow up assessment (mean difference: 3.9 points (95% CI, 1.1–6.8); adjusted p = 0.007) (Bourke *et al.*, 2011, Bourke *et al.*, 2014). Similarly, when the intervention was tested as an RCT, the intervention arm experienced clinically relevant improvements in FACT-F scores at 12 weeks compared to the control arm (mean difference: 5.3 points; 95% CI,2.7–7.9; adjusted p < 0.001). Changes were maintained following withdrawal of supervision at six months (mean difference: 3.9 points; 95% CI, 1.1–6.8; adjusted p = 0.007). However, clinically relevant improvements in disease specific QOL at three months (adjusted mean difference: 8.9 points; CI 3.7–14.2) were not sustained after the cessation of the supervised period (adjusted mean difference: 3.3 points; 95% CI, 2.6 to 9.3).

1.4.3.7. Animal Studies

Jones et al. (2012) investigated the effects of exercise on cancer progression and mechanisms of metastasis in an orthotopic model of murine prostate cancer. Mice were randomly assigned to exercise group who completed voluntary wheel-running, (*n* = 28) or a non-intervention control (*n* = 31) groups. Median running distance ranged from ∼4 to ∼6 km/day. The primary tumour growth rate, measured by the modulation of circulating host levels of metabolic and sex-steroid hormone levels, improvements in immune surveillance, and reduced systemic inflammation and oxidative damage, was comparable between the exercise and control group across the entire course of the experiment, demonstrating that exercise did not inhibit primary cancer progression. However, exercise did favourably alter genes responsible for metastatic dissemination in the primary tumour, with a shift toward reduced metastasis (Jones *et al.*, 2012a).

A second study used an in vivo model to investigate the role of skeletal mechanical stimuli on the development and osteolytic capability of secondary breast tumours. For loading, the left limbs of mice were subjected to dynamic compressive loading for two or six weeks using an established protocol (1200 cycles at 4 Hz, 5 days/week); non-loaded control mice only underwent anaesthesia. Mechanical loading was found to inhibit the growth and osteolytic capability of secondary breast tumours (Lynch *et al.*, 2013). There may also be an application of the findings of this study in human populations, where compressive loads (induced by specific loading exercise programmes) inhibit the growth of tumours, however this area requires further exploration.

1.4.4. Discussion

Studies prescribing exercise for patients living with metastatic cancer report high levels of patient tolerance, acceptability and adherence. Importantly, no adverse events related to exercise interventions were reported among any of the interventions reviewed. Statistically significant and clinically meaningful improvements in exercise behaviour, muscle strength, aerobic fitness, walking speed and muscle mass were observed with several different exercise training modalities. Importantly, these benefits occurred without aggravating symptoms such as fatigue and bone pain. Physical exercise programmes tailored to the individual patient are safe, efficacious and feasible in this

population. This review has identified key factors which should be considered when prescribing exercise to patients living with bone metastases.

Patient Assessment and Eligibility

As advised in patients with early stage cancer, a review of each patient's history and physical examination of cardiac, pulmonary, neurological, and musculoskeletal signs and symptoms should be used to assess the safety of exercise interventions, or the need for further evaluation (Jones *et al.*, 2010). In particular, a pain assessment should also be included for patients with bone metastases, including pain interference with function which may be measured using the BPI. Fracture risk is a key consideration. Studies reviewed reporting adverse events did not find a high fracture incidence with exercise versus control or an association between exercise and fracture risk. However, fracture risk assessments would allow greater risk stratification for this group of patients and may allay the fears of health professionals regarding exercise prescription. Tools such as Mirel's Classification Score or the FRAX calculator may prove useful for determining suitability to exercise, however as seen in the exercise interventions reviewed, such tools are rarely used to guide patient eligibility for exercise interventions. Instead, performance scales or predictions of survival length are commonly utilised in order to determine participant eligibility, which may exclude patients who can exercise safely and stand to gain from increasing activity levels. A number of studies considered for inclusion in this review listed evidence of bone metastases in the hip or spine (Segal *et al.*, 2003, Stevinson and Fox, 2006, Galvao *et al.*, 2010, Winters-Stone *et al.*, 2014), or evidence of bone metastases in the spine alone (Kuehr *et al.*, 2014) (but included other stage IV participants), brain or bone metastases (Quist *et al.*, 2012, Quist *et al.*, 2015) as exclusion criteria for participation. The inclusion of patients with bone metastases in exercise studies would have greatly increased the generalisability of results to all patients at this stage of disease. Additionally, a number of exercise studies in advanced cancer did not specify if patients with metastatic bone disease were included (Oldervoll *et al.*, 2006, Rummans *et al.*, 2006, Cheville *et al.*, 2010) or specify the site of metastases (Carson *et al.*, 2007). Further detail regarding patients' disease status would enable clinicians to ascertain the applicability of study results to specific patient populations in practice.

Exercise Prescription and Instruction

Papers reviewed describe a number of approaches to exercise prescription in this population. The key concepts underpinning individualised exercise prescription and adapting exercises to patient ability were reinforced in all papers reviewed. The

heterogeneity of patients presenting with bone metastases means that exercise prescription will vary widely according to the patient's presentation. Some patients present late in the course of their metastatic disease, after failing all treatment modalities, whereas others present without a known primary diagnosis. The purpose of exercise prescription or desired outcomes will inform the programme prescribed. Furthermore, patients with metastatic bone disease experience pain, compromised bone health etc. which, as discussed, complicate exercise prescription. For patients living with metastatic prostate cancer, autoregulation has been introduced as a novel concept. This allows patients to self-determine their capabilities at each session collaboratively with the supervising exercise specialist (Hart *et al.*, 2017). It is clear therefore that individualised exercise prescription is required when treating patients with bone metastases to manage unique patient presentations and multifaceted issues.

From the exercise interventions reviewed, different approaches to exercise individualisation are described. The most prescriptive approach outlines a systematic method of prescribing resistance exercise based on the location of bone metastases to ensure affected regions are not targeted and mechanical force at areas of metastases is minimised (Figure12) (Galvão *et al.*, 2011, Cormie *et al.*, 2013). This approach has considerable potential to be used to guide exercise programmes in the clinical setting. Additionally, circuit exercise classes tailored to individuals and exercise programme determined by baseline functional ability have also been prescribed with no exercise related adverse events (Oldervoll *et al.*, 2011, Litterini *et al.*, 2013). This emphasises the importance of clinical reasoning to inform exercise adaptation suitable for metastatic bone disease.

Tailored exercise instructions were described in many studies, such as providing tuition on correct exercise techniques, monitoring effective techniques and providing guidance on exercise intensity by monitoring heart rate and perceived exertion (Porock *et al.*, 2000, Oldervoll *et al.*, 2006, Bourke *et al.*, 2011). Litterini et al. (2013) advised numerous safety precautions to accommodate patients' medical history, comorbidities, treatment-related side effects, venous access devices, peripheral neuropathy, pathologic fracture risk, immunosuppression, lymphedema risk, and/or cardiopulmonary issues (Litterini *et al.*, 2013). For example, participants who had pain with lower extremity weight bearing or who had compromised spinal integrity exercised by walking in a lap in a pool. This also emphasises the role that clinical exercise specialists such as physiotherapists can play in exercise prescription for patients with bone metastases. Given the expertise required to ensure safe exercise practice in this cohort, large scale exercise

interventions, e.g. community exercise referral schemes, may have a limited role in this population. The elements of study design described above appear essential in providing exercise programme for patients with bone metastases, namely the use of oncology-trained exercise specialists who are able to complete complex assessments and evaluations of patient response to exercise. In the absence of consensus guidelines, these specialists may be best placed to apply research knowledge into clinical practice and individually tailor exercise for this complex cohort.

Future Areas for Exploration

Exercise may have a role in improving the bone health of patients with metastatic cancer. Where previously exercise was assumed to cause an increased risk of fracture, there is the possibility and transference that undertaking individual prescribed exercise could lower fracture risk in patients. Interventions in the current review describe improvements in bone mineral content and bone turnover markers with both aerobic and resistance exercise training (Rief *et al.*, 2016). Additionally, animal studies suggest that the mechanical loading of bone involved with exercise may inhibit osteolytic capability and formation of metastatic tumours. Findings indicate the exciting possibility of prescribing exercise to attenuate the progression of bone metastatic disease (Lynch *et al.*, 2013). There is a need to look at the effect of exercise on markers of bone turnover and radiological imaging in subsequent studies involving human participants with bone metastases in order obtain a greater understanding of skeletal adaptions to exercise in this population.

Future trials involving larger sample sizes of patients living with bone metastases are planned to expand these preliminary findings of feasibility studies included in this review (Galvão *et al.*, 2011). A study protocol for a randomised pilot trial involving differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastases under concomitant radiotherapy is currently ongoing. The planned trial aims to show that strengthening of the paravertebral musculature does not only have positive effects on the perception of pain, but may also improve QOL and fatigue in patients with unstable spinal metastases (Welte *et al.*, 2017). A protocol for another trial exploring resistance exercise and the suppression of tumour growth in advanced prostate cancer patients with sclerotic bone metastases has also been published (Hart *et al.*, 2017). This study will further enhance knowledge surrounding the effect of exercise on systemic markers of metastases. The forthcoming INTERVAL Trial, part of the Movember Global Prostate Cancer, Exercise and Metabolic Health Initiative, may also contribute much knowledge in the area of exercise and metastatic disease (Saad *et al.*, 2016). This

initiative will involve a global multi-centre exercise trial for men with advanced cancer looking at overall survival as an endpoint. Additional endpoints will include measures of strength, physical function and physical activity and will focus on the mechanisms of action underpinning the relationship between physical activity and the biology of advanced disease.

1.4.5. Conclusion

Exercise interventions for patients with bone metastases are associated with positive physical and self-reported outcomes and a low rate of adverse events. Exercise prescription in patients with bone metastases does involve complex decision making however a number of tools are available which may inform both assessment and exercise prescription. There is a need for further studies involving exercise interventions for patients with metastatic cancer. There is also a need for studies of greater duration, which assess the effects of longer term exercise interventions, to assess the sustainability of exercise interventions in this population. Additionally, there is a need to examine both supervised and non-supervised exercise interventions in this population, and determine the effect of both interventions on patients' quality of life.

Despite the need for further studies in this area, exercise appears to be an effective adjunct therapy in the advanced cancer context, however, evidence of effectiveness alone does not imply that an intervention should be adopted in clinical practice. The decision about whether an intervention should be implemented in clinical practice should be based on large, randomized, controlled trials and thresholds for risk and safety (Sheldon et al. 1998). Knowledge distillation, that is the synthesis of findings from the most rigorous research available on a specific topic into systematic reviews and guidelines, has begun in the area of physical activity and metastatic disease, with the publication of the Physical Activity Guidelines for Patients with Metastatic Cancer (Macmillan.org.uk, 2019, Straus *et al*. 2009). Although there remains gaps in the literature, the publication of Macmillan guidelines, and the evidence synthesised within, forms the basis for closing the evidence-practice gap around physical activity and advanced cancer (Morris et al. 2011).

Healthcare professionals such as clinicians and physiotherapists may be instrumental in recommending exercise to patients and referring patients to exercise services. The literature completed in the previous section identified patients with bone metastases are

often excluded from exercise interventions. Further exploration of the views of healthcare professionals is necessary, to ensure current knowledge reflects the growing body of evidence supporting the benefits of exercise in the metastatic population.

1.5. Thesis Aims and Objectives

There is a growing body of evidence supporting the health benefits associated with physical activity in advanced stages of cancer (Titz *et al.*, 2016). However, a central issue for understanding the potential impact of physical activity exposure, or dose, on health outcomes in an advanced cancer population is the ability to engage these patients in physical activity programmes. Therefore, it is necessary to examine the evidence surrounding the recruitment and adherence of patients with advanced cancer to exercise trials. In addition, as exercise intervention studies are labour, cost, and time-intensive, and there is a need to examine the attrition of patients living with advanced cancer on exercise interventions in order to optimise future study designs (Chapter 2). It is also important to identify the factors which may play a role in the illness experience of metastatic cancer patients and which may contribute to physical inactivity. As this patient group are living with incurable cancer, the perceived burden of exercise may differ from patients living with earlier stage cancer, and can be further complicated by long-term treatment related side effects. Barriers and facilitators to physical activity will be explored through qualitative interviews examining the views of men diagnosed with metastatic prostate cancer (Chapter 4). This may help to identify factors which can encourage increased physical activity participantion post advanced cancer diagnosis (Orji *et al.*, 2012), such as exericse consultations and advice. While there is increasing evidence to support the therapeutic benefits of exercise clinically there are many barriers to exercise prescription and participation and referral pathways for cancer rehabilitation are scarce. Most clinicians do not routinely discuss physical activity with patient's post-cancer diagnosis (Daley *et al.*, 2008) and referral to physical rehabilitation is not a part of the standard care of patients diagnosed with cancer in Ireland. Health professionals such as consultants and physiotherapists may be important sources of motivation, encouraging patients with advanced cancer to increase physical activity levels, and there is a need to investigate the attitudes of health professionals working in Ireland towards recommending physical activity to the advanced cancer cohort (Chapters 5a and 5b). With the increasing emphasis placed on survivorship in the new national cancer strategy, increased knowledge in the area of cancer rehabilitation for patients with all stages of disease will inform the implementation of research findings into clinical practice.

As described previously, patients with bone metastases are often excluded from exercise programmes due to concerns of pathological fracture. There is a need for further exercise trials in the advanced cancer cohort to explore mechanisms behind the psychological and physical effects of exercise (Chapter 6). Biological samples will be collected from the ExPeCT trial, recruiting participants living with metastatic cancer. This thesis will examine on the secondary outcomes of the trial, specifically investigating if a low-cost, accessible 6 month exercise programme can improve the QoL and other lifestyle factors of men with advanced cancer. This evidence may strengthen the argument for all patients with metastatic disease to undertake physical activity programmes.

Overall Aim: To investigate the role of physical activity in metastatic disease.

1. To determine if patients with advanced cancer can adhere optimally to exercise interventions in order to gain maximum benefits.

Objective:

- To systematically review the recruitment, adherence and attrition rates of patients with metastatic cancer participating in exercise interventions and examine components of exercise programmes that may affect these rates (Chapter 2).

2. To examine the attitudes and beliefs of health professionals and patients towards physical activity and advanced cancer.

Objectives:

- To examine the attitudes of patients living with advanced prostate cancer towards physical activity (Chapter 4).
- To investigate Irish chartered physiotherapists' views regarding physical activity and advanced cancer, with a specific focus on providing physical activity recommendations (Chapter 5a).

- To determine the beliefs of a national sample of oncologists regarding physical activity and patients with advanced cancer, to explore any potential concerns clinicians have in relation to physical activity in this population (Chapter 5b).

3. To determine if the evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism in obese men with prostate cancer.

Objectives:

- To determine the effects of a six month exercise intervention on the quality of life of men with advanced prostate cancer (Chapter 6).
- To determine the effects of a six month exercise intervention on sleep, pain, depression, stress, physical function and physical activity levels in men with advanced prostate cancer (Chapter 6).
- To determine the adherence of men with advanced prostate cancer to a six month exercise intervention (Chapter 6).

*Note: This thesis will examine secondary outcomes of the ExPeCT trial. The primary outcome of the trial is circulating tumour cells, and the aims and objectives of the larger EXPECT trial are:

To determine whether

- Platelet cloaking of PrCa circulating tumour cells is more prominent in men with - obesity than without.
- The degree of platelet cloaking varies with levels of systemic and primary tumour inflammation and coagulability.
- Expression of an obesity-associated lethality gene signature leads to variation in platelet cloaking.

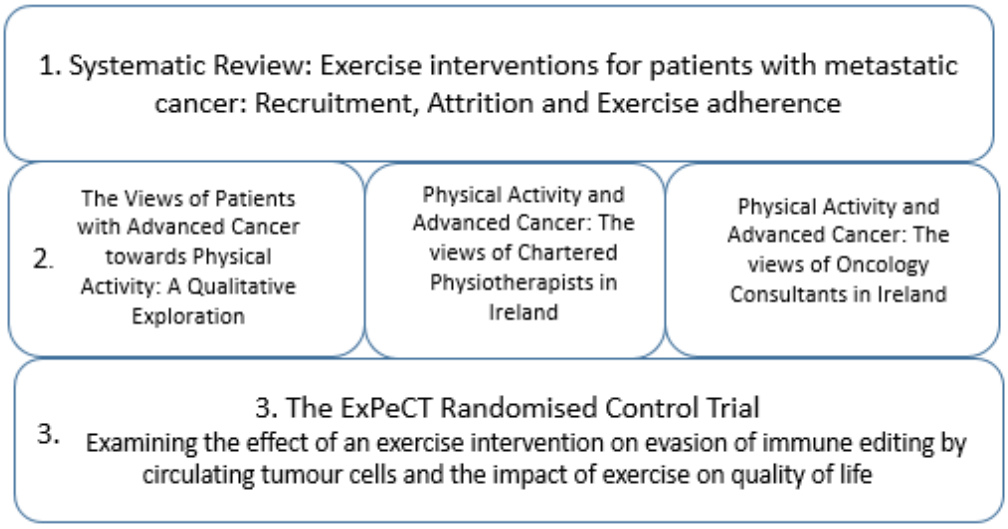


Figure 13 Overview of Phd Thesis

2. Chapter 2: Materials and Methods

This chapter will describe the study designs, sampling methods and measurement methods to be investigated in the studies in this thesis. An introduction to data analysis is also presented. Details of the methodologies of individual studies are presented in the results chapters (Chapters 4 to 6).

2.1. Qualitative Methodology

Descriptive studies, including qualitative and mixed method designs, were used in this thesis (Chapters 4 and 5). Qualitative research in its most basic form involves the analysis of any unstructured data or "any kind of research that produces findings not arrived at by means of statistical procedures or other means of quantification" (Corbin and Strauss, 1990). After determining a research question the next step is to choose the most useful study methodology or way to collect and treat data (Grbich, 2012). Qualitative methodologies are not a single research approach, but different epistemological perspectives and pluralism have created a range of approaches such as grounded theory, phenomenology, ethnography, action research, narrative analysis, and discourse analysis (Vaismoradi *et al.*, 2013). Qualitative methods were used in Chapter 4 to explore the views of patients living with bone metastases towards exercise. While qualitative methodologies are primarily exploratory and descriptive, quantitative investigations test for group differences, variable relationships, and causal explanations (Blessing and Forister, 2012). The two approaches are often complementary in healthcare studies. When both types of investigation are employed concurrently, the study is termed a mixed-methodological study (JW, 2012). This is an emergent methodology which is increasingly used by health researchers, especially within health services research (Tariq and Woodman, 2013). The underlying assumption of mixed methods research is that it can address some research questions more comprehensively than by using either quantitative or qualitative methods alone. Additional advantages of a combined approach include enhancing the validity of research findings and increasing the capacity to cross check one data set against another. Mixed methods research was used in this thesis to explore the views of healthcare professionals on the role of physical activity for patients with advanced cancer (Chapter 5a and 5b).

2.1.1. Study Designs

There are many approaches to data collection in qualitative research, with interview and observation being the most common. Qualitative interviews were used in this thesis. Interviews can be carried out as the primary research strategy or in conjunction with observation or other techniques. In most qualitative research, the degree to which interviews and observations are structured varies. For example, when conducting interviews, the researcher could use a very detailed interview protocol, a general topic guide with eight to 12 broad questions and probes, or utilise neither (e.g. conduct a very open-ended interview) (Devers and Frankel, 2000). The advantages of interviews over other qualitative methods is that the interviewer has the opportunity to probe or ask follow-up questions and, while they are time consuming and resource intensive for the researcher, they are generally easier for the respondent, particularly when opinions or impressions are being sought.

Several factors influence the degree of structure or type of instrumentation used in a qualitative research study. The first factor is the purpose of the study. When the study is more exploratory or attempting to discover and/or refine theories and concepts, a very open-ended protocol may be appropriate. The second is the extent of existing knowledge about a subject. How much is known and how transferable is the knowledge to the case being studied? Unstructured interviews can be time-consuming and difficult to manage, and to participate in, as the lack of predetermined interview questions provides little guidance to participants (Gill et al. 2008). The third factor, the resources available, particularly subjects' time, and the number and complexity of cases, can affect the degree of structure or instrumentation. Finally, the type of feedback or mode of sharing research results agreed upon and the timeframe for doing so, may affect the instrumentation required. Structured instruments facilitate quicker data analysis and reporting of results. The danger in highly structured studies however, is finding what is expected and/or settling upon an explanation too early (Devers and Frankel, 2000).

The study presented in Chapter 4 of this thesis used semi-structured interviews, organised around an interview guide. An interview guide often contains topics, themes or areas to be covered during the course of the interview. Questions are designed to be open ended and flexible, and are directed towards discovering the who, what where and how of events and experiences (Sandelowski, 2000). This allowed participants to tell their own story in their own way and prevented structures being put on answers. An

alternative methods of data collection is to conduct focus groups, group discussions on the topic of physical activity and cancer. However, it was felt participants may not have discussed their feelings and opinions openly in this forum. Additionally, given the wide geographical dispersion and varying occupational statuses of potential participants included in the Chapter 4, individual interviews, as opposed to focus groups, were deemed the most feasible data collection method in this population.

2.1.2. Qualitative Sampling

Sampling in qualitative research, as in the quantitative approach, is focused on the application of findings beyond the research sample. Qualitative research does not aim at securing confidence intervals of studied variables around exact values in a population but typically tries to sample broadly enough and to interview deeply enough that all the important aspects and variations of the studied phenomenon are captured in the sample (Miles and Gilbert, 2005).

As for the sample size, qualitative research does not use power analysis to determine the needed *n*, but instead most commonly uses the criterion of saturation (Strauss and Corbin, 1998), which means adding new cases to the point of diminishing returns, when no new information emerges. In order to satisfy the saturation criterion, the most common sampling strategy used in qualitative research is purposeful sampling. This allows the identification and selection of information-rich cases related to the phenomenon of interest. Criterion sampling, a type of purposeful sampling strategy, is most commonly used in implementation research (Palinkas *et al.*, 2015). Purposive sampling strategies are designed to enhance understandings of selected individuals or groups' experience(s) or for developing theories and concepts. Researchers seek to accomplish this goal by selecting "information rich" cases, that is individuals, groups, organisations, or behaviours that provide the greatest insight into the research question (Devers and Frankel, 2000). This sampling type was used for studies in this thesis (Chapter 4). While quantitative methods rely on established formulae for avoiding Type I and Type II errors, qualitative methods often rely upon precedents for determining the number of participants based on type of analysis proposed (e.g. 3-6 participants interviewed multiple times in a phenomenological study versus 20-30 participants interviewed once or twice in a grounded theory study), level of detail required, and emphasis of homogeneity (requiring smaller samples) versus heterogeneity (requiring larger samples) (Guest *et al.*, 2006).

2.1.3. Qualitative Reliability and Validity

Reliability refers to the degree to which an outcome measurement is free of random error (McDowell, 2006). If a measurement lacks reliability, then the data obtained may be useless because of error (Blessing and Forister, 2012). Reliability is based on the idea that knowledge is relative and dependant on all of the contextual features of the people, place, time and other circumstances (Taylor and Francis, 2013). Reliability can be addressed in qualitative research in several ways (Silverman 2005). For example, reliability can be enhanced if the researcher obtains detailed field notes, uses tape recording, and transcribes the tape recording. In qualitative health science research reliability often refers to the stability of responses to multiple coders of data sets (Creswell and Poth, 2017). Intercoder agreement should be assessed between coders on transcript data, either as agreement on code names, the coded passages, or the same passages coded the same way.

Writers have searched for and found qualitative equivalents that parallel traditional quantitative approaches to validation (Creswell and Poth, 2017). Measures for ensuring validity in qualitative research involve asking the participants to confirm that the interpretations represent, faithfully and clearly, what the experience was/is like for the people acting as sources of information in the research. Four primary validation criteria proposed are credibility (Are the results an accurate interpretation of the participants' meaning?); authenticity (Are different voices heard?), criticality (Is there a critical appraisal of all aspects of the research?); and integrity (Are the investigators self-critical?) (Whittemore *et al.*, 2001). These questions encourage the researcher to raise questions about the ideas developed during a research study.

2.1.4. Qualitative Data Analysis

Qualitative content analysis is one of the several qualitative methods currently available for analysing data and interpreting its meaning (Elo *et al.*, 2014). By using content analysis, it is possible to analyse data qualitatively and at the same time quantify the data (Grbich, 2012). The aim is to attain a condensed and broad description of the phenomenon, and the outcome of the analysis are concepts or categories describing the phenomenon. Content analysis involves three main phases: preparation, organisation,

and reporting of results. The preparation phase consists of collecting suitable data for content analysis, making sense of the data, and selecting the unit of analysis. This can be a word or a theme. The organisation phase includes open coding, creating categories, and abstraction (Elo and Kyngas, 2008). Each individual data set (e.g. transcriptions of interviews) is reviewed for overall content. Content refers to the key themes or ideas that are overtly identifiable, with reference to the research question that underpins the study (Taylor and Francis, 2013). These initial themes generally direct the next stage of analysis, such as re-reading the text and allocating segments of text to named codes. All the generated codes are again reviewed and like codes are grouped as a concept.

Content analysis (Elo and Kyngas, 2008)	
Preparation	Being immersed in the data and obtaining the sense of whole, selecting the unit of analysis, deciding on the analysis of manifest content or latent content
Organising	Open coding and creating categories, grouping codes under higher order headings, formulating a general description of the research topic through generating categories and subcategories as abstracting
Reporting	Reporting the analysing process and the results through models, conceptual systems, conceptual map or categories, and a storyline.

Table IV Content analysis phases and their description

2.1.5. Qualitative Methods in this Thesis

A variety of qualitative methods are used in this thesis. Chapter 4 uses semi-structured interviews to examine the views of patients towards physical activity in patients living with advanced cancer. In addition, qualitative methods were used as part of a mixed methods design in Chapter 5 to explore the views of physiotherapists and clinicians towards physical activity in this population. Online surveys were created, which included ten attitude questions based on the guiding principles of the Health Belief Model (Janz and Becker, 1984), and two case study questions. The case study approach is

particularly useful to employ when there is a need to obtain an in-depth appreciation of an issue, event or phenomenon of interest, in its natural real-life context (Crowe *et al.*, 2011). Two contrasting case studies were chosen as they were based on typical presentations of patients with bone metastases seen previously in an outpatient oncology clinic in a national cancer centre. Participants received the survey by e-mail. While there are limitations to administering surveys via the internet e.g. the selection of participants may be biased to those with internet access and there may have been no e-mail address directory for some healthcare professionals, it was felt this method of communicating with participants was most feasible for the studies in this thesis (Klein, 2002). The advantages of using an internet survey for these studies is that potential participants were spread widely geographically around Ireland but had nearly universal access to the internet. Additional advantages were that online questionnaires require less time for responses and follow-up communication and eliminate the need for manual data entry. Additionally, the online instrument used in this thesis can maintain anonymity of the survey.

2.2. Quantitative Methodology

2.2.1. Study Design

The study design and consequent study type are major determinants of a study's scientific quality and clinical value (Rohrig *et al.*, 2009). Study designs in medicine can generally be divided into those that are observational and those that are experimental. Studies may also be prospective or retrospective in design. In prospective studies, data collection is planned in advance, whereas retrospective studies examine data that already exists. The use of records that have already been collected, particularly those stored in an electronic database, means that retrospective cohort studies can be relatively cheap, quick, and easy to perform and provide information on very large sets of data eg. a population based study (Sedgwick, 2014). Compared to retrospective designs, prospective designs are credited with having better control of variables and a greater possibility of having valid and reliable standardised measurement methods. Disadvantages include cost and difficulty extrapolating the results of strictly controlled methods to the clinical setting where similar levels of control are not possible (Blessing and Forister, 2012).

An observational study is a type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome, i.e. no treatment is given (NCI, 2017). Examples of observational studies include case-control studies and cross-sectional studies. In case-control studies the prevalence of exposure to a potential risk factor(s) is compared between cases and controls. If the prevalence of exposure is more common among cases than controls, it may be a risk factor for the outcome under investigation. A cross-sectional study examines the relationship between disease (or other health related state) and other variables of interest as they exist in a defined population at a single point in time or over a short period of time (e.g. calendar year) (Blessing and Forister, 2012). The major limitation of observational studies is the inability to control for confounding variables such as age, socio-economic status, health status, smoking and alcohol habits. While statistical methods can control for these variables, there is always a risk that observed effects may be due, not to the condition under study, but to other factors which are unknown to those carrying out the research. Despite this, observational studies have several important roles in medical research and are very useful as early descriptors in under researched populations.

In an experimental study, investigators study the impact of varying some factor that they can control, on the outcome of interest. Experimental studies are less susceptible to confounding because objective methods are introduced to determine who is exposed and who is unexposed. True experimental designs are characterised by the random selection of participants and the random assignment of the participants to groups in the study. Stratification is also common in clinical trials, and assures that compared groups are similar with respect to known prognostic factors (Kernan et al. 1999). In multicenter trials, such as ExPeCT, participants can be stratified based on gender, age categorized, and baseline disease severity.

A randomised controlled trial (RCT) is considered the gold standard of experimental research and is one of the main study designs used in this thesis (Chapter 6). There are several important features of an RCT. Firstly, randomisation ensures patients will be allocated to the different groups in a balanced manner. This may be done in many ways, including randomisation tables or computer assisted random sequencing. Randomisation also ensures that possible confounding factors, such as risk factors, comorbidities and genetic variabilities, will be distributed by chance between the groups (structural equivalence) (Rohrig *et al.*, 2009). Additionally, patients are normally analysed within the group to which they were allocated, irrespective of whether they

experienced the intended intervention (intention to treat analysis) (Sibbald and Roland, 1998).

Blinding refers to the concealment of group allocation from one or more individuals involved in a clinical research study (Karanicolas *et al.*, 2010). Allocation concealment is necessary in RCT's to ensure researchers are unable to predict the group to which a patient will be randomised until the patient is unambiguously registered on study and researchers are unable to change a patient's allocation after they are randomised. Similarly, patients should ideally remain unaware of their treatment allocation until the study is completed, as knowledge of group assignment may affect their behaviour in the trial and their responses to subjective outcome measures. Trials that blind several groups of individuals including both the participant and the assessor, are referred to as "double-blinded". However, trials involving the double-blinding of participants are often not feasible for studies involving exercise interventions. In this case the limitations and potential biases introduced by the lack of blinding should be acknowledged in any subsequent publications.

The main advantage of RCT's is that they provide better control over possible bias through randomisation and blinding, i.e. high internal validity. RCT's are the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome. Other study designs cannot rule out the possibility that the association was caused by a third factor linked to both intervention and outcome (Sibbald and Roland, 1998). RCT design does have some drawbacks depending on the research question and how the studies are conducted. In other circumstances, an RCT may be ethical but infeasible due to difficulties with randomisation or recruitment. A waitlist control group is also a reasonable design but does introduce potential bias given the sense of expectancy it creates in the control group (Kinser et al. 2013) A third limiting factor is that RCTs are generally costlier and more time consuming than other studies. Careful consideration therefore needs to be given to their use and timing (Sibbald and Roland, 1998).

2.2.2. Quantitative Sampling

The main methodological issue that influences the generalisability of clinical research findings is the sampling method (Elfil and Negida, 2017). Sampling procedures help to

ensure that the individuals taking part in the research are representative of the population of interest.

Researchers use two major sampling techniques: probability sampling and non-probability sampling. Probability sampling, also known as random sampling or representative sampling, is based on the fact that every member of a population has a known and equal chance of being selected. With probability sampling, a researcher can specify the probability of a particular participant being included in the sample. When random sampling is used, each element in the population has an equal chance of being selected (simple random sampling) or a known probability of being selected (stratified random sampling). An example of a simple random sampling process would involve assigning numbers to all subjects and then using a random number generator to choose random numbers for inclusion. An example of a stratified random sampling process would involve splitting subjects into mutually exclusive groups and then using simple random sampling to choose members from groups. These techniques create samples that are highly representative of the population.

With non-probability sampling, there is no way of estimating the probability of participants being included in a sample (Badia, 2005). Non-probability sampling is a sampling technique where the samples are gathered in a process that does not give all the individuals in the population equal chances of being selected. While non-probability sampling may be representative of the sampling frame, it cannot depend on the rationale of the probability theory and therefore these studies have an inherent bias. Common non-probability sampling methods include; convenience sampling, quota sampling, purposive sampling and self-selected sampling. Convenience sampling was used in the randomised controlled trial in this thesis. This is a technique that uses an open period of recruitment that continues until a set number of subjects, events, or institutions are enrolled. Here, selection is based on a first-come, first-served basis. This approach is used in studies drawing on predefined populations, such as participants in medical clinics (Luborsky and Rubinstein, 1995). While non-probability samples may not be representative of wider populations they can be useful for informing pilot or exploratory studies and may be required due to issues including expense or time constraints (Schreuder *et al.*, 2001).

The calculation of an adequate sample size, the number of participants in a sample, is the process of calculating the optimum number of participants required to be able to

arrive at ethically and scientifically valid results (Kadam and Bhalerao, 2010). Generally, the sample size for any study depends on the following (Kirby *et al.*, 2002):

- Acceptable level of significance (α). The conventional values used for *a* are 0.05 and 0.01.
- Standard deviation in the population (σ). This is obtained from previous studies or a pilot study. The larger the standard deviation, the larger the sample size required for the study.
- The power of the study (δ)
- The expected effect size
- The underlying event rate in the population
- Sample size is calculated using the following formula:

$$n = \frac{2(Z_{\mathrm{a}} + Z_{1-\beta})^{2}\sigma^{2},}{\Delta^{2}}$$

In this formula, *n* is the required sample size. For Z_{α}, *Z* is a constant (set by convention according to the accepted α error and whether it is a one-sided or two-sided effect). For Z1-β, Z is a constant set by convention according to power of the study. In the above-mentioned formula σ is the standard deviation (estimated) and Δ the difference in effect of two interventions which is required (estimated effect size) (Kadam and Bhalerao, 2010). This gives the number of sample per arm in a controlled clinical trial.

The ExPeCT trial aimed to recruit 200 participants over the lifetime of the study, evenly divided between the exercise group and the control group. A power calculation was performed, based on the primary outcome measure of platelet cloaking. Data was used from a previous study of ovarian cancer cell lines which showed approximately 2% platelet adhesion (Egan et al. 2011). A standard deviation (SD) varying from 2% to 10% was set, to enable detection of a difference in platelet cloaking of between 0.79% and 3.9%.

2.2.3. Reliability and Validity

2.2.3.1. Reliability

Random errors may occur during any part of the measurement process and may be a product of inattention, fatigue or inaccuracy (Stokes, 2011). Absolute reliability is expressed as the standard error of the measurement and is expressed in terms of the actual unit of the original instrument. The relative reliability of an instrument is reported in three ways, the inter-rater reliability, intra-rater reliability and instrument reliability (Stokes, 2011). Inter-rater reliability indicates the consistency in measurements among individuals taking the measurements. Intra-rater reliability indicates the consistency with which an individual takes measurement. Instrument reliability indicates the consistency of measurement by a particular instrument.

Cronbach's alpha, the most widely used objective measure of reliability, provides a measure of the internal consistency of a test or scale (Blessing and Forister, 2012). It is expressed as a number between 0 and 1. Additionally, the concept of intra-rater reliability is of great importance when considering the reproducibility of clinical measurements. For continuous data, the intra-class correlation (ICC) is the measure of choice (Stokes, 2011). For nominal data, the kappa coefficient of Cohen and its many variants are the preferred statistics (Gwet, 2014). The coefficient ranges from 0 to 1. The lower the error of variance the higher the correlation coefficient, such that at 1 no measurement error occurs.

2.2.3.2. Validity

Validity is defined as the extent to which a test measures that which it is intended to measure or the range of interpretations that can be appropriately placed on a measurement score (McDowell, 2006). Content validity refers to comprehensiveness or to how adequately the questions selected cover the themes that were specified in the conceptual definition of its scope i.e. whether the test is broad enough to address the scope of the content. Criterion validity considers whether scores on the instrument agree with a definitive, gold standard measurement of the same theme (Stokes, 2011). Criterion validity may be divided into concurrent and predictive validity, depending on whether the criterion refers to a current or future state. For variables such as pain, quality of life, or happiness, gold standards do not exist and thus validity testing is more

challenging. For such abstract constructs, validation of a measurement involves a series of steps known as construct validation. Construct validity is determined by how well the study controls for experimental bias and expectations, or the degree to which the measurement is based on theory (Blessing and Forister, 2012, Carter and Lubinsky, 2015). Aspects of criterion and construct validity are measured using validity coefficients such as Pearson-product moment correlation, Spearman's rank order correlation, Kendall's rank order correlation or the phi coefficient. Construct validity can also be analysed using factor analysis.

2.2.4. Principles of Quantitative Data Analysis

2.2.4.1. Descriptive statistics

Descriptive Statistics are used to describe the basic features of the data in a study. They provide simple summaries about the sample and the measures, and form the basis of quantitative analysis of data (Trochim and Donnelly, 2001). When summarising data using descriptive methods, the key concepts are measures of central tendency and measures of variability. The most commonly used measures of central tendency are the mean, median and mode. Measures of variability commonly reported in biomedical research include the range, standard deviation, interquartile range and standard error of the mean (Blessing and Forister, 2012).

2.2.4.2. Inferential statistics

Following a descriptive review of the data the researcher may then look to test the study's null hypothesis using interferential statistics. Most studies will look for a relationship between one or more variables or a difference between two variables (Blessing and Forister, 2012). In many cases, the conclusions from inferential statistics extend beyond the immediate data alone (Trochim and Donnelly, 2001).

In statistical testing, a significance level is chosen, called alpha (α). By convention, the α level is set at .05 or .01 (e.g. a<.05). When the data are analysed, the statistical test yields a p value. This is the probability that the observed results could occur by chance if the null hypothesis is true. If the $p < \alpha$ the null hypothesis is rejected. If $p > \alpha$ the null hypothesis is retained. If an α level of .05 is set, then a confidence interval of 95% is

used. Confidence intervals represent a range of scores, which contains the true population mean at specified levels of probability (Miles and Gilbert, 2005). For example, if the relative risk in a study is 7 and the 95% confidence interval is 3.5, the researcher can be 95% confident that the actual relative risk is between 3.5 and 10.5 (7 ± 3.5).

Further statistical tests can then be chosen based on the study design and the types of data. Choosing the right test can add power to study findings and provide strong support for outcomes and conclusions (Blessing and Forister, 2012). Tests may include t-tests, to test the differences between two groups' means if data is parametric or alternatively the non-parametric equivalent, a Mann-Whitney test, could be used. Regression analysis may also be used. Regression analysis, ANOVA (analysis of variance) and ANCOVA (analysis of covariance) are all subsumed under the general linear model. This statistical method of predicting dependent variable variability by one or more independent variables is the method of statistical analysis used in Chapter 6 (Stokes, 2011).

2.3. The ExPeCT Trial

2.3.1. Overview of the ExPeCT trial

The ExPeCT trial (Exercise, Prostate Cancer and Circulating Tumour Cells), an international multicentre prospective study, recruited men with metastatic Prostate Cancer from five Irish hospitals and one UK hospital (Guy's and St Thomas's, London, the Mater Misericordia Hospital Dublin, Beaumont Hospital Dublin, St. James's Hospital Dublin, Tallaght Hospital Dublin and St. Luke's Radiation Oncology Network, Dublin). The ExPeCT Trial was funded by the World Cancer Research Fund. Cancer Trials Ireland was the sponsor for the Irish sites on the study (Protocol Number CTRIAL-IE (ICORG) 15-21).

The overall aim of the ExPeCT Trial was to show that a low-cost, accessible exercise programme can improve QoL and potentially ameliorate the effects of obesity through alterations in the systemic adipokine and inflammatory mediator profile. Obesity, known to be associated with a pro-inflammatory, pro-thrombotic humoral milieu, confers a worse prognosis in prostate cancer (PrCa). Circulating tumour cells (CTCs) are identified in the blood in advanced cancer. Their quantitation provides prognostic information. "Cloaking" of CTCs by adherent platelets impedes Natural Killer (NK)-cell clearance of

CTCs from the circulation, enhancing metastatic spread. NK-cell function in blood and in solid organs is quantitatively and qualitatively reduced in obesity. Platelet cloaking may be enhanced in obesity due to the pro-inflammatory, pro-thrombotic state, and may be a mechanism for worse cancer-specific outcomes in this group. Obesity and its biochemical effects may be influenced by lifestyle changes such as exercise. Physical activity reduces levels of systemic inflammatory mediators and so aerobic exercise may represent an accessible and cost-effective means of ameliorating the pro-inflammatory effects of obesity. The ExPeCT trial incorporated both an observational component and an exercise component, with randomisation of participants to either an exercise or control group. All participants completed a number of lifestyle measures at T0, T3 (3 months) and T6 (6 months) (Figure 14).

My role on the ExPeCT trial included co-ordinating patient recruitment, protocol management, data management, clinical assessments and delivering the exercise programme. I was lead author on the publication of the ExPeCT Trial study protocol, published in the journal Trials (Appendix 7). A number of secondary outcomes from the trial are examined in this thesis (Figure 15). ExPeCT will be reported in Chapter 6 according to CONSORT guidelines (Moher *et al.*, 2001). The following section outlines the methodologies used to gather data for this thesis.

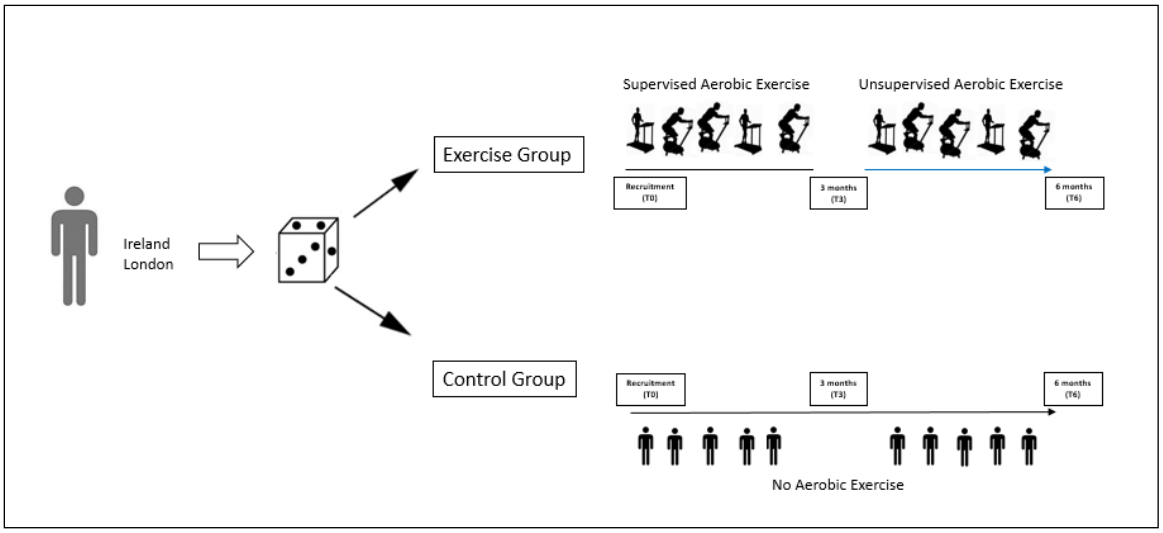


Figure 14 ExPeCT Trial Study Design

			Study Period			
			Enrolment	T0	T3	T6
		Eligibility Screen	X			
		Informed Consent	X			
		Allocation	X			
Type of Data	**Details Collected**	**Instrument Used**				
Demographic and Clinical Measures	Background Details	Physicians' Health Study Assessment		X	X	X
	Blood Pressure, BMI, Waist Circ.	Clinical Registration Form		X	X	X
Lifestyle Measures	Subjective Physical Activity	Physicians' Health Study Assessment		X	X	X
	Objective Physical Activity Measurements	Actigraph Accelerometers		X		
	Diet (dairy products, meat, vitamin D)*	Physicians' Health Study Assessment		X	X	X
Psychosocial Measures	Sleep	Pittsburgh Sleep Quality Index		X	X	X
	Memory and Cognition	Physicians' Health Study Assessment		X	X	X
	Pain	Brief Pain Inventory Scale		X	X	X
	Depression	PHQ-9		X	X	X
	Quality of Life	FACT-P		X	X	X
	Stress	Perceived Stress Scale – 4		X	X	X
	Adherence to Exercise Programme	FT7 Polar Monitors, Patient Exercise Diaries		X	X	X
Biological* Measures	Circulating Tumour Cells	ScreenCell® system		X	X	X
	Serum and Plasma	Vacuette® system		X	X	X
	Natural Killer Cells	Vacuette® system		X	X	X
	Diagnostic Paraffin Tissue Blocks	Original diagnostic NCB paraffin tissue blocks	X			

Figure 15 ExPeCT Spirit Figure

Outcomes analysed as a part of this thesis

* The ExPeCT Trial is a large RCT with multiple endpoints. Biological samples and diet information were gathered as part of the overall ExPeCT programme however this data was not analysed as part of this thesis.

2.3.2. ExPeCT Patient Details

2.3.2.1. Patient Datasheet

A datasheet was completed for each participant after recruitment at T0 and at the T3 and T6 follow-up visits. Data gathered included date of birth, blood pressure, routine laboratory data (serum prostate specific antigen (PSA), haemoglobin, white cell and platelet counts, site of metastasis and cancer-related data (stage and Gleason grade of cancer, details of current and previous systemic and radiation therapy).

2.3.2.2. Demographic Details

Participant demographic details were collected using a form adapted from the Harvard Health Professionals Study. This form collected details regarding marital status, race, living situation, work status and smoking and alcohol consumption. Additional information was collected to determine patients' co-morbidities and regular medications.

2.3.2.3. BMI, Blood Pressure and Waist Circumference

A number of techniques, such as bioelectrical impedance, dual x-ray absorptiometry and total body water, can measure body fat, but there may be challenges to the routine use of these measures in clinical practice. Body mass index (BMI), weight adjusted for height, is a practical and widely used method to screen for obesity which was used in this thesis (Force, 2003). BMI provides a measure of overall adiposity, but the distribution of adipose tissue in predicting health risks associated with obesity is also important. BMI values are age-independent and the same for both sexes (WHO, 1995).

Body weight was measured, to the nearest 0.1 kg on the SECA. Participants were measured in one layer of light clothing. Standing height was measured using a portable SECA 763 stadiometer (Figure 16).

Figure 16 SECA 763 Stadiometer

Participants were asked to stand, without shoes, on the footplate, with their back against the stadiometer, legs together, arms down by their sides and mid-axillary line in parallel to the stadiometer. The headboard was lowered until it touched the crown of the head, compressing the hair. Measurements were taken to the nearest 0.1 cm. BMI was calculated by dividing weight in kg by height in meters squared (kg/m^2). BMI was classified into obese (≥30 kg/m^2), overweight (≥ 25 kg/m^2) and normal categories (18.50 - 24.99 kg/m^2) (WHO, 1995).

Abdominal fat deposition is generally considered to be a key component of obesity (Ford *et al.*, 2003). Despite the widespread use of waist circumference measurements, there remains no uniformly accepted measurement protocol, resulting in a variety of techniques employed throughout the published literature (Mason and Katzmarzyk, 2012). However, the measurement of waist circumference is a simple anthropometric indicator of metabolic and cardiovascular disease risk, and a convenient way of measuring abdominal fat deposition. Waist circumference was measured using a non-stretch flexible tape placed directly on the skin at the midpoint between the superior border of the iliac crest and the lowest rib, following normal expiration (WHO, 2011). The tape was checked to ensure it was positioned perpendicular to the long axis of the body and parallel to the floor.

2.3.3. ExPeCT Physical Activity Measures

2.3.3.1. Measurement of Exercise Adherence

The WHO defines adherence as “the extent to which the persons’ behaviour (including medication-taking) corresponds with agreed recommendations from a healthcare provider” (Sabaté, 2003). Adhering to an exercise programme enhances its effectiveness, and patients who undertake regular physical activity may be less likely to progress to recurrent, persistent, or disabling problems (Hayden *et al.*, 2005). The multi-dimensional nature of exercise adherence can be difficult to measure, including completing exercise and physical activity correctly, in different settings and at the agreed ‘dose’, accurate measurement of exercise adherence (Holden *et al.*, 2014). Currently none of the available methods can be considered as a gold standard and a combination of methods is recommended (Farmer, 1999). Moreover, the most appropriate measure of adherence for one type of therapeutic exercise (for example specific body-region exercises for strengthening and flexibility) may not be appropriate to measure adherence to other types of therapeutic exercise, such as increasing general physical activity levels (Holden *et al.*, 2014). Therefore, the RCT in this study collected exercise adherence data in two ways:

1) Polar heart rate monitors, worn by the patient for every exercise session undertaken.

2) Physical activity diaries, as described in section 2.3.4.1

Polar FT7 heart rate monitors (Polar Electro, Lake Success, NY) (Figure 17) provided data regarding patients’ heart rates during exercise (average and maximum values) as well as the time spent exercising. Polar monitors have been shown as accurate and valid for measuring heart rate when compared to an ECG recording (Terbizan *et al.*, 2002). The test–retest reliability (intra-class correlation coefficient and 95% confidence interval) for the FT7 tools at rest is 0.84 [0.78–0.89] (Mitchell *et al.*, 2016). Data from the monitor can be uploaded to an online platform and used to determine the number of exercise sessions patients completed each week, the duration of these sessions and the rate of exertion reached. These measurements were used to assess patient adherence to the exercise intervention. Adherence to both the supervised exercise classes and home exercise programmes were analysed using both Polar monitor results and exercise logbooks. Patients were considered fully adherent if they achieved both the target heart rate (intensity) and duration of exercise prescribed. The mean values of these two dimensions (intensity and duration) of adherence were combined to give an overall

adherence percentage .Participants also completed self-reported measures of physical activity and sedentary behaviour at T0, T3 and T6 (Section 2.3.4.1).

Figure 17 Polar FT7 Heart Rate Monitor

2.3.4. ExPeCT Patient Reported Outcomes

In addition to clinical and demographic information, and objective measures of physical activity, a number of patient reported outcomes were collected as secondary outcomes of the ExPeCT Trial. Secondary outcomes may be chosen in randomised controlled trials for exploratory purposes in order to develop a hypothesis for future research (Macefield *et al.*, 2014). Secondary outcomes were also used in the ExPeCT trial in order to measure and evaluate the additional effects of the intervention.

As a result of the increasing focus on patient reported outcomes, several hundred measures are now available, and for many diseases there is often great choice as to what measure should be used (Garratt *et al.*, 2002). Patient reported outcomes are unique indicators of impact of disease on the patient, helpful in empowerment of the patients, necessary for determination of efficacy of the treatment and are useful in the interpretation of clinical outcomes and treatment decision making (Acquadro *et al.*, 2003). The appropriate selection of an outcome measure should be guided by evidence of measurement properties, for example reliability and validity, as described previously, as well as responsiveness, and practical properties, such as patient acceptability and feasibility (McDowell and Newell, 1996). These properties were examined for each of

the measures included in the ExPeCT Trial. A number of measures including quality of life, sleep, depression and stress were used and are outlined below.

2.3.4.1. Subjective Measurement of Physical Activity

In addition to objective measures of physical activity, self-reported instruments are commonly used to assess physical activity (Sylvia *et al.*, 2014). A self-administered physical activity questionnaire derived from the Harvard Health Professional's Study was completed by participants in the ExPeCT trial (Appendix 12) Studies have demonstrated this questionnaire is reproducible and provides a useful measure of average weekly activity, particularly vigorous activity (Chasan-Taber *et al.*, 1996). The intra-class correlation coefficients used to measure reproducibility were 0.39 for inactivity, 0.42 for non-vigorous activity, and 0.52 for vigorous activity. The correlations between diary-based and questionnaire-based activity scores, adjusted for variation in the diary measurements, were 0.41 for inactivity, 0.28 for non-vigorous activity, and 0.58 for vigorous activity. The questionnaire measures the average weekly time spent at four sedentary activities (watching television, sitting at home, sitting at work, sitting in transit) and 10 specified activities (walking or hiking outdoors, jogging, running, bicycling, swimming, tennis, squash or racquet- ball, other aerobic exercise, weight lifting, and outdoor work) during the past year. There are 13 response categories ranging from none to ≥40 hours per week. In addition, the average daily number of flights of stairs climbed is recorded (Chasan-Taber *et al.*, 1996). The number of hours spent on each of the activities and inactivity is multiplied by its intensity, defined in multiples of the metabolic equivalent of sitting quietly for an hour (MET), to arrive at a measure of average weekly energy expenditure attributable to the activity or inactivity. One MET, for an adult of average weight, is approximately 210 mL of oxygen uptake per kg of body weight. A compendium of physical activities was used to assign METs for each activity. Activities with MET values of six or higher are considered vigorous, and activities with MET values less than six were considered non-vigorous (Ainsworth *et al.*, 2011). In addition, all participants completing the exercise arm of the RCT in this thesis completed weekly exercise diaries.

Numerous limitations of self-reports have been discussed in the literature (Sallis and Saelens, 2000). Social desirability bias can lead to over-reporting of physical activities and may prove difficult for populations with particular memory and recall skill limitations (Sallis and Saelens, 2000). Self-report measures of physical activity have shown to be

both higher and lower than directly measured levels of physical activity. This poses a problem for both reliance on self-report measures and for attempts to correct for differences between self-report and direct measures (Mcclain *et al.*, 2007). However, subjective measures are also cheap and simple to implement compared to objective measures, and are useful for large-scale population studies.

2.3.4.2. Measurement of Sleep

Polysomnography (PSG) is the gold standard for assessing sleep. This involves individuals spending the night in a sleep laboratory under continuous supervision of a sleep technician. PSG is labour intensive, time-consuming, expensive, and requires highly trained personnel (Manzar *et al.*, 2015). Actigraphy, the measurement of wrist movements, is also used to assess sleep or waking state through an accelerometer in a wrist worn device (Girschik *et al.*, 2012). However, self-report remains the most practical method for epidemiologic studies attempting to collect information on large population-based samples as self-report measures are low cost and relatively non-obtrusive to the patient's sleep experience (Girschik *et al.*, 2012). Epidemiologic studies have found that sleep duration is associated with obesity, diabetes, hypertension and mortality. Sleep duration has become a potentially important and novel risk factor for chronic disease. (Lauderdale *et al.*, 2008). It was also important to examine sleep in the ExPeCT population, as sleep disturbances are associated with disease progression, quality of life and anxiety in patients living with advanced cancer (Hlubocky et al. 2017).

In this thesis, sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire, which assesses sleep quality and disturbances over a 1-month time interval (Appendix 12). Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. A *Global Sleep Quality* score greater than 5 discriminates between good and poor sleepers and yields a diagnostic sensitivity of 89.6% and specificity of 86.5% (Buysse *et al.*, 1989). The clinimetric and clinical properties of the PSQI, suggest its utility both in clinical practice and research activities, including the evaluation of sleep disorders in cancer patients (Akman *et al.*, 2015). The Cronbach's *a* of 0.83 obtained for PSQI components indicates a high degree of internal homogeneity (Buysse *et al.*, 1989).

2.3.4.3. Measurement of Stress

Psychological stress focuses on individuals' subjective evaluations of their ability to cope with the demands posed by specific events or experiences (Brown, 1974). There is no universally-accepted definition of stress and no gold standard measurement either in the lab or in the field (Hovsepian *et al.*, 2015). The psychological impact of stress can be measured through observation, checklists, self-report methods, and interviews (Figueroa-Fankhanel, 2014). Self-report measures of stress are the most commonly used method to assess stress in the field (Hovsepian *et al.*, 2015).

The Perceived Stress Scale – 4 (PSS), was used to measure stress in the ExPeCT Trial (Appendix 12). This self-report scale provides a measure of the degree to which situations in one's life are appraised as stressful. When used within the context of a stress model, the PSS has the potential to identify the role of perceived stress in important cancer outcomes, such as patients' quality of life and adherence to treatment (Golden-Kreutz *et al.*, 2004).

There are three versions of the PSS. The 10- and 14-item self-report PSS instruments have established reliability and validity (r=0.85) (Cohen *et al.*, 1983). The questions of the measure are quite general in nature and hence relatively free of any content specific to one sub-population. The limited four-item abridged PSS scale used in this thesis suffers in internal reliability (r=.60) and provides a less adequate approximation of perceived stress levels than the larger scales, however it is appropriate for use in situations requiring a very brief measure of stress perceptions (Cohen *et al.*, 1983). The test-retest reliability and predictive validity of the measure is strongest for shorter time periods.

2.3.4.4. Measurement of Depression

Depression is defined by a cluster of behaviours and symptoms that have both mental and physical manifestations, and affect a wide range of functionality (Yard and Nelson, 2013). The use of clinician-rated depression scales in routine clinical practice is costly and puts additional requirements on clinicians' training and consultation times. It has therefore been suggested that cheaper self-report instruments may replace clinician-rating scales in routine practice, and studies have determined there is a moderate-to-strong correlation between clinician-rated scales and self-report questionnaires (Rush *et al.*, 2006).

The PHQ 9 Depression Measure was used to assess the mental health of ExPeCT patients (Appendix 12). This is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders (Kroenke *et al.*, 2001). Self-report measures of depression are generally most useful as screening procedures since their false-positive rate is usually lower than their false-negative rate (Endicott, 1984).

The PHQ 9 measure consists of the actual 9 criteria upon which the diagnosis of Diagnostic and Statistical Manual of Mental Disorders -IV depressive disorders is based (Kroenke *et al.*, 2001). In addition to making criteria-based diagnoses of depressive disorders, the PHQ 9 is also a reliable and valid measure of depression severity. These characteristics plus its brevity make the nine item PHQ-9 a useful clinical and research tool (Kroenke *et al.*, 2001). A PHQ-9 score ≥10 has a sensitivity of 88% and a specificity of 88% for major depression. The internal reliability of the PHQ-9 is also excellent, with a Cronbach's α of 0.89 (Kroenke *et al.*, 2001).

The PHQ-9 also performs well in testing depression in cancer patients (Hinz *et al.*, 2016) and is a valid tool for use with this population (Thekkumpurath *et al.*, 2011). The traditional cut-off for general populations using the PHQ-9 is ≥ 10, however the American Society of Clinical Oncology panel recommended a cut-off score of ≥ 8 for patients living with cancer, based on a study of the diagnostic accuracy of the PHQ-9 with cancer outpatients. A meta-analysis of the measure in a cancer population also supports the ≥ 8 cut-off score (Andersen *et al.*, 2014).

2.3.4.5. Measurement of Quality of Life

The assessment of health-related quality of life (QOL) is an essential element of healthcare evaluation, as QOL scores demonstrate the difference or the gap between the hopes and expectations of an individual and that individual's present experience (Coons *et al.*, 2000). In the advanced cancer population it is particularly important to determine the quality of life as patients with progression of cancer frequently experience multiple symptoms, economical burden, home management problems and lack of emotional well-being, all of which can adversely affect QOL (Miller and Walsh, 1991).

There are two basic types of health related QOL measurement: generic and disease/population specific. Generic measures are not designed to identify important, disease specific dimensions or for detecting important clinical changes. Disease or population specific measures contain domains and dimensions that are designed to be valid only for a specified condition or population. Disease specific measures, therefore, maximise content validity and provide for greater sensitivity and specificity; however they cannot be used to compare health related QOL across conditions or populations (Jenney and Campbell, 1997).

QOL measurement in prostate cancer therapy has become an essential component of clinical trial evaluation. In many instances, the goal of therapy in prostate cancer is one of palliation as opposed to cure, making it essential to assess the impact these treatments have on QOL and use this knowledge in the overall evaluation of treatment efficacy. The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire is a relevant, worldwide tool used for assessing the health related QOL in men with prostate cancer and was used to measure the quality of life of ExPeCT patients (Appendix 12) (Esper *et al.*, 1997).

The FACT-P questionnaire consists of 12 prostate cancer specific questions added to the general (FACT-G) instrument, thereby comprising a 47-item questionnaire. Questions cover five domains; ‘physical well-being’, ‘social/family well-being’, ‘emotional well-being’, ‘functional well-being’ and ‘additional concerns’ (items relating specifically to prostate cancer and/or its treatment). Each item can be answered on a 5-point (0–4) scale. Scores for the whole questionnaire can range between 0 and 156 (Stone *et al.*, 2008). Internal consistency of the prostate cancer subscale ranges from 0.65 to 0.69, with Cronbach coefficients for FACT-G subscales and aggregated scores ranging from 0.61 to 0.90. The European Organization for Research and Treatment (EORTC) QLQ-C30 quality of life questionnaire is one of the most widely used instruments in oncology. It assesses the physical, psychological and social functions of people living with cancer,

and has been used in palliative care populations (Groenvold et al. 2006). This measure could have been used as an alternative measure of quality of life in the ExPeCT trial. Finally, the McGill Quality of Life Questionnaire would also have been appropriate, as this questionnaire is relevant to all phases of the disease trajectory for people with a life-threatening illness, such as the participants in ExPeCT (Cohen et al. 1995).

2.3.4.6. Measurement of Memory

Data suggests subjective memory complaints (SMCs), such as trouble following a group conversation or finding one's way around familiar streets, are associated with objective cognitive status (Amariglio *et al.,* 2011). SMCs may reflect early, subtle cognitive changes and are associated with personality traits and meaning-in-life in healthy, older adults (Steinberg *et al.,* 2013). Additionally, while cancer and associated treatments may impair cognitive functioning across many domains (eg. processing speed), memory deficits may be particularly relevant (Ehlers *et al*., 2018). The ExPeCT study included a measure of subjective memory complaints from the Harvard Health Professionals Follow-up study (Amariglio *et al.,* 2011). A continuous variable was created for participants' total number of self-reported memory complaints.

2.4. Ethical Approval

The ExPeCT study protocol and other documentation were approved by NRES Committee London - Camden & Islington (REC reference 14/LO/1859), The Mater Misericordia Hospital Research Ethics Committee, Dublin (REC reference: 1/378/1760), Beaumont Hospital Ethics (Medical Research) Committee, Dublin (REC Reference 15/73), SJH/AMNCH Research Ethics Committee, Dublin (REC Reference: 2014-11 List 41 (6)) and St Luke's Radiation Oncology Network, Dublin (REC Number not assigned. Trial referred to as ICORG 15-21 (sponsorship identifier)). Letter of approval are included in Appendix 2.

ExPeCT also received sponsorship from Cancer Trials Ireland for the Irish sites on this study (Protocol Number CTRIAL-IE (ICORG) 15-21).

The protocol for the qualitative study involving patients (Chapter 4) was granted by St. James's Hospital / Adelaide Meath National Children's Hospital research ethics

committee. The protocol for studies involving clinicians and physiotherapists (Chapters 5a and 5b) was approved by the Trinity College Faculty of Health Sciences Ethics Committee.

3. Chapter 3: A systematic review of exercise interventions for patients with metastatic cancer: Recruitment, Attrition and Exercise adherence

3.1. Introduction

As described in Chapter 1, there is a growing body of evidence detailing the many benefits of staying active through all stages of the cancer continuum (Courneya and Friedenreich, 2007). These benefits include lower fatigue levels, improved functional capacity, greater independence and increased quality of life (Beaton *et al.*, 2009, Salakari *et al.*, 2015, Dittus *et al.*, 2017). Increasingly patients with advanced cancer (including metastatic cancer), are encouraged to stay physically active and partake in exercise programmes, reflecting research in this area (Eyigor *et al.* 2014). The symptoms of advanced disease, including fatigue, pain, dyspnoea and nausea may lead to low physical activity levels, or even inactivity, and in turn reduce physical functioning (Oldervoll *et al.*, 2006), making participation in exercise programmes very challenging (Albrecht and Taylor, 2012). It follows therefore that, symptoms may also adversely affect the recruitment and retention rates of patients with advanced cancer to exercise trials, however currently these rates are poorly understood. Examining the participation of patients with advanced cancer in exercise trials is essential as difficulties with patient recruitment and retention can decrease the statistical power of trials, as well as trial integrity and validity (Scianni *et al.*, 2012).

Persons with advanced cancer are now living longer than in previous decades (Cheville *et al.*, 2010). For example, the estimated five year survival rate in patients diagnosed with advanced prostate cancer is 30%-46% (Cormie *et al.*, 2013). These values represent an increase in survival from the 26.5% reported in the 1980's (Silverberg *et al.*, 1990). Similarly, the five year survival rates of women with advanced breast cancer is now 22%, an increase from 16% in in the 1980s (American Cancer Society, 2017, Silverberg *et al.*, 1990). Previously the maintenance and recovery of physical function in patients with limited life expectancy received little attention (Oldervoll *et al.*, 2006). Patients with advanced cancer may have been provided with palliative rather than restorative interventions (Porock *et al.*, 2000). As patients are now living longer, the need for rehabilitation to help counteract the adverse effects of long-term systemic treatments on strength, fatigue and physical functioning is increasingly recognised. Many rehabilitation plans include structured exercise programmes. The rates of uptake,

adherence and completion of exercise programmes reported in cancer populations vary, suggesting that not all patients find it an acceptable or practical therapy (Maddocks *et al.*, 2009). If exercise is to be developed as a therapy suitable for all patients with advanced cancer, a greater understanding of the limitations to its use is needed.

Recruitment of patients with cancer to exercise trials has been described as particularly challenging and time consuming (Sygna *et al.*, 2015). Detailed recruitment data for patients with early stage cancer (Courneya *et al.*, 2008) is available; however, there is less information on the recruitment and retention of patients with advanced stage cancer. It is suggested that many established barriers to recruitment (e.g. travel distance to centres and lack of interest) reported in healthy populations also exist in patients with advanced cancer, as well as barriers associated with a later stage of disease (e.g. multiple hospital appointments). Patient adherence to treatment regimens for conditions that are very complex, such as cancer, can be as low as 30% (Jin *et al.*, 2008). It is imperative to determine if patients with advanced cancer can adhere optimally to exercise interventions in order to gain maximum benefits.

Given the differences between persons living with localised disease and those living with advanced disease, results of previous systematic reviews involving localised cancer are not generalisable to persons with advanced cancer (Beaton *et al.*, 2009). The purpose of this systematic review is to examine the recruitment, attrition and adherence rates of advanced cancer patients to exercise programmes. This review may also help to aid the development of structured exercise programmes tailored for the advanced cancer population. The retention of participants in exercise trials has also shown to be influenced by how studies are designed and conducted, e.g. visit frequency and study length (Yu, 2013). This review will also examine different components of exercise programmes that may have an association with trial recruitment and retention. This review may also help to aid the development of structured exercise programmes tailored for the advanced cancer population.

Chapter Aims and Objectives:

Aim:

To systematically review the involvement of patients with advanced cancer in exercise interventions.

Objectives:

- To investigate the recruitment, adherence and attrition rates of patients with advanced cancer participating in exercise interventions
- To determine the features of exercise programmes associated with recruitment and attrition rates including exercise frequency, duration, intensity and type of exercise.

3.2. Methods

3.2.1. Inclusion Criteria

3.2.1.1. Types of participants

Studies were included if the participants were defined by the author of the trial as having advanced cancer. Advanced cancer (also known as metastatic or palliative) cancer includes the AJCC definition of Stage IV advanced cancer (Edge and Compton, 2010).

3.2.1.2. Types of interventions

Exercise was defined as planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness (Martin *et al.*, 2000). Only studies that prescribed structured exercise training were included. Studies consisting of general physical activity recommendations or advice were excluded. Studies involving adult survivors of paediatric cancers were excluded. Studies involving yoga, breathing techniques, relaxation or meditation only as the exercise intervention were also excluded.

3.2.2. Search Strategy

Pubmed, Cochrane, PsychINFO and CINAHL databases were searched for articles up to December 2017 for studies relating to exercise programmes in patients with advanced disease.

The search keywords ‘adherence’, ‘exercise’, ‘advanced’ and ‘cancer’ were used in varying combinations. ‘Adherence’ was supplemented with the associated terms

'motivation' and 'compliance', 'retention', 'co-operation', 'attrition', 'tolerance', 'participation' and 'engagement' and 'exercise' was supplemented with 'physical activity', 'aerobic activity', 'fitness' or 'training'. Articles were required to have an original full-text available in English.

3.3. Data Extraction and Quality Assessment

3.3.1. Data extraction

The titles and abstracts of all included studies were screened for relevance concerning the research topic. Two authors (G.S. and L.B.) independently assessed the identified titles and abstracts and made proposals to include or exclude these articles. A third author (E.G.) made the final decision based on the inclusion and exclusion criteria. Each reviewer assessed the studies for levels of evidence and methodological quality.

Data extracted included primary tumour site, the number of people screened and recruited, recruitment period, reasons for declining recruitment, the number of patients randomised, the number allocated to exercise, number of dropouts, reason for dropout and adverse events. Exercise data extracted included exercise type, frequency, intensity, duration and session length. Data extraction was completed by two authors (G.S. and L.B.) using an adapted version of the Cochrane extraction form (Furlan *et al.*, 2009) that was piloted on two studies. Any discrepancies were resolved by referring to the original papers and by discussion.

3.3.2. Assessment of methodological quality

The methodological quality of articles was assessed by two independent reviewers using the PEDro scale for systematic reviews and the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies. Randomised controlled trials (RCTs) were considered of excellent quality when they were rated 8 to 11 on the PEDro scale; good quality when rated from 6 to 8; moderate quality when rated from 4 to 5; and scores <4 were low quality RCTs. The Newcastle-Ottawa scale (NOS) evaluates three domains: selection, comparability and outcome, with a score of > 7 indicating good methodological quality (Viswanathan *et al.*, 2008). Ratings were performed by both authors (GS and LB)

and any disagreements were resolved by consensus through discussion with a third author (EG).

The Oxford Centre for Evidence Based Medicine (J. Howick) Levels of Evidence provided a scale for stratifying evidence from strongest to weakest on the basis of susceptibility to bias and the quality of the study design.

3.3.3. Definitions

A number of terms were used in the following review:

- Recruitment Rate: The number of eligible participants recruited onto a clinical trial (Chang *et al.*, 2004).
- Adherence: The extent to which a person's behaviour corresponds with agreed recommendations from a health care provider in a clinical trial (Jack *et al.*, 2010).
- Attrition: The loss of eligible participants from clinical trials at any time following consent to participate (Siddiqi *et al.*, 2008).

3.4. Data Analysis

Percentage rates were calculated for proportions of eligible patients entering an exercise study on being approached and, when allocated to an active study arm, completing the programme. The characteristics of the sample were described using means, standard deviations, frequencies, and percentages. All predictor variables were analysed using Pearson r correlations including the relationship between the independent variables such as programme frequency and length and the dependent variables of recruitment and attrition. A p value of $<.05$ was regarded as statistically significant. Calculations were performed using Statistical Package for the Social Sciences version 19.0.

3.5. Results

A total of 2,153 studies were originally identified by the search terms in Pubmed (n=90 articles), PsychINFO (n=470 articles), Embase (n=1117 articles) and CINAHL (n=476 articles) databases, with a further 222 additional records identified through other sources.

1,855 articles remained when duplicates had been removed. Titles of articles were screened leaving 684 articles for abstract review. Finally 149 articles remained for full text reading. Authors of 18 studies were contacted for further information to determine disease stage of included participants. In the absence of a response these studies were excluded. 124 studies were excluded at this point leaving 18 articles eligible for review. A PRISMA flowchart outlines the study identification process (Figure 18).

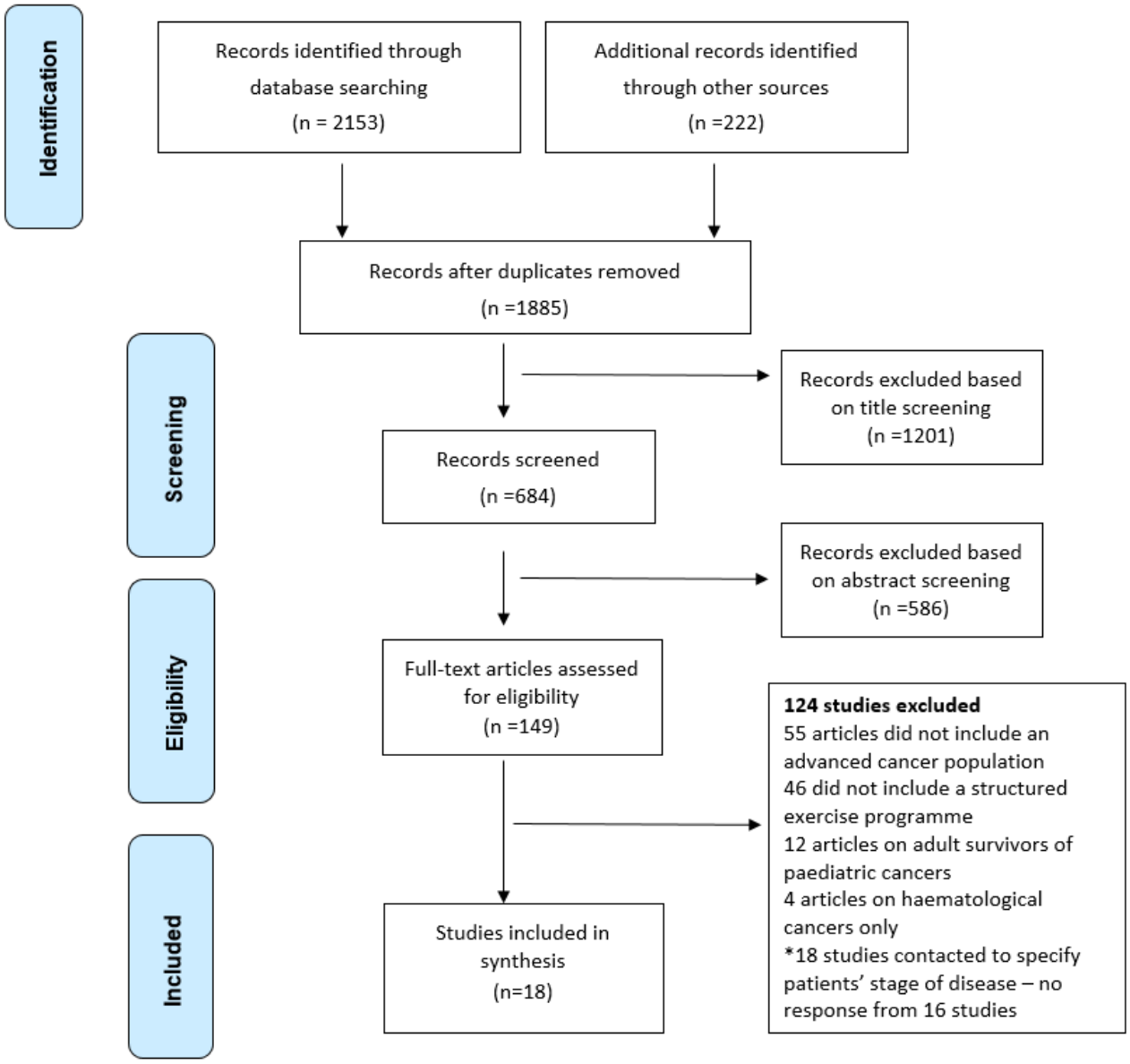


Figure 18 PRISMA Flowchart

3.5.1. Study Characteristics

The 18 included studies are summarised in Table IV. Ten of these were RCTs, the remaining studies were feasibility studies (n=4) and pilot studies (n=4) with single-arm designs. The mean sample size of the intervention groups was 32 (range 7-121) patients. The included trials involved a total of 952 participants. The mean age of

participants ranged from 49.3 to 73.1 years. Participants completed the exercise intervention in groups in 14 of the 18 trials reviewed. Four exercise interventions were offered as a part a broader lifestyle intervention. There was a mean PEDro score of 7.4 for randomised controlled trials. Three studies were of excellent quality (Bourke *et al.*, 2011, Oldervoll *et al.*, 2011, Uster *et al.*, 2017). Level two was the highest level of evidence of the trials included.

Study	Site of Primary Cancer	Type of Study	Quality Assessment	Level Of Evidence OCEBM
Bourke et al. (2011)	Prostate Cancer	RCT	Excellent	Level 2
Cheville et al. (2010)	GI + other	RCT	Good	Level 2
Chiarotto et al. (2017)	GI, Breast, Lung + other	Feasibility study	Good	Level 3
Cormie et al. (2013)	Prostate Cancer	RCT	Good	Level 2
Galvão et al. (2017)	Prostate Cancer	RCT	Good	Level 2
Headley et al. (2004)	Breast Cancer	RCT	Good	Level 2
Hwang et al. (2012)	Lung Cancer	RCT	Good	Level 2
Jensen et al. (2014)	GI Cancer	Feasibility Study	Good	Level 3
Ligibel et al. (2015)	Breast Cancer	RCT	Good	Level 2
Litterini et al. (2013)	Breast + other	Pilot Study	Good	Level 2
Lowe et al. (2013)	GI + other	Pilot Study	Good	Level 4
Oldervoll et al. (2006)	GI + other	Pilot Study	Good	Level 3
Oldervoll et al. (2011)	GI + other	RCT	Excellent	Level 2
Quist et al. (2012)	Lung Cancer	Feasibility Study	Good	Level 3
Temel et al. (2009)	Lung Cancer	Feasibility Study	Good	Level 3
Uster et al. (2017)	GI and Lung Cancer	RCT	Excellent	Level 2
van den Dungen et. al. (2014)	Breast, GI + other	A pilot study	Good	Level 3
Zimmer et al. (2017)	Colorectal Cancer	RCT	Good	Level 2

*Note: GI: GastroIntestinal Cancer

Table V Overview of Included Studies

3.5.2. Exercise Interventions

Table V details the exercise interventions included. Seventeen trials required participants to attend supervised exercise sessions, and one study required that participants exercise unsupervised (Headley *et al.*, 2004). All exercise programmes prescribed some aerobic exercise. Fifteen of 18 trials reviewed included resistance exercise training. Pre-exercise testing was completed as part of the screening process in two studies, both in patients with primary lung cancer (Temel *et al.*, 2009, Hwang *et al.*, 2012). Three further studies completed cardio-pulmonary testing as a primary outcome measure (Bourke *et al.*, 2011, Quist *et al.*, 2012, Jensen *et al.*, 2014).

The methods used to measure and monitor aerobic exercise intensity varied widely, making it difficult to determine relationships between exercise intensity and trial recruitment and attrition rates. The majority of trials prescribed moderate to vigorous intensity activity, and monitored exercise intensity by percentage heart rate maximum (Bourke *et al.*, 2011, Galvao *et al.*, 2017), Vo2 peak (Hwang *et al.*, 2012) and the Borg Breathlessness Scale (Temel *et al.*, 2009, Zimmer *et al.*, 2018). The target of heart rate maximum ranged from 55% to 85% while peak workload targets ranged from 60% to 80%. Intensity set by the Borg Breathless Scale ranged from 11 to 15. Seven trials provided no details as to how aerobic exercise intensity was measured (Headley *et al.*, 2004, Oldervoll *et al.*, 2005, Oldervoll *et al.*, 2006, Cheville *et al.*, 2010, Lowe *et al.*, 2013, Chiarotto *et al.*, 2017, Uster *et al.*, 2017). In trials prescribing resistance exercise, 11 out of 15 programmes recorded exercise training parameters including weight, sets and repetitions. All but three trials prescribed resistance training between 60% and 90% of 1 repetition maximum (Temel *et al.*, 2009, Quist *et al.*, 2012, Jensen *et al.*, 2014, van den Dungen *et al.*, 2014, Uster *et al.*, 2017, Zimmer *et al.*, 2018). One trial prescribed resistance exercise of sets of 8-15 repetitions to fatigue (Litterini *et al.*, 2013). The remaining trials prescribed two to four sets of 12-8RM or three sets of 10-12 RM (Cormie *et al.*, 2013, Galvao *et al.*, 2017).

Study Name	n	n (Exercise Intervention)	Recruitment Period	Length of Programme	Exercise Intervention Details	Adherence Rates
Bourke et al. (2011).	50	25	Not reported	12 weeks	Aerobic and Resistance 30 mins 3 times weekly AI: 55-85% max HR RI: Not stated	Supervised: 95% Unsupervised: 87%
Cheville et al. (2010).	115	49	Not reported	8 weeks	Resistance 30mins 3 times weekly RI: Not stated	89%
Chiarotto et al. (2017)	35	35	29 months	Indefinite – lasted as long as the patient wished to participate	Aerobic and Resistance 75 mins once weekly AI: Not stated RI: 2 sets of 10 reps	73.1% (95% CI 67.0-79.4)
Cormie et al. (2013).	20	10	12 months	12 weeks	Resistance 60mins twice weekly RI: 2-4 sets of 12-8 RM	93.2+-6%
Galvão et al. (2017)	57	28	36 months	12 weeks	Resistance, Aerobic and Flexibility 60 mins 3 times weekly AI: 60-85% max HR RI: 3 sets of 10-12 RM FI: 2-4 reps 30-60 sec hold	89%
Headley et al. (2004).	38	19	Not reported	12 weeks	Aerobic 30 mins twice weekly AI: Not stated	75%
Hwang et al. (2012).	24	12	7 months	8 weeks	Aerobic 30-40 mins 3 times weekly AI: 80% Vo2 Peak	83% Mean 71.2% Median 83.3% Range 4.2–100%
Jensen et al. (2014).	26	26	Not reported	12 weeks	Aerobic or Resistance 45 mins twice weekly AI: 60-80% predetermined pulse RI: 2-3 sets of 15-25 reps 60-80% 1RM	Resistance arm:72% Aerobic arm: 59%

Ligibel et al. (2015)	101	48	54 months	16 weeks	Aerobic Exercise Goal of 150 mins per week AI: Moderate Intensity	Not reported
Litterini et al. (2013)	66	34	25 months	10 weeks	Aerobic or Resistance Exercise 30 to 60 mins Twice weekly AI: 10 to 12 RPE RI: 1 set of 8 to 15reps to fatigue	70%
Lowe et al. (2013).	9	9	6 months	6 weeks	Aerobic and Resistance Individualised to each patient AI: Not stated RI: Not stated	87%
Oldervoll et al. (2006).	34	34	Not reported	6 weeks	Aerobic and Resistance 50 mins 2 weekly AI: Not stated RI: Not stated	88%
Oldervoll et al. (2011).	231	121	30 months	8 weeks	Aerobic and Resistance 50 mins twice weekly AI: Not stated RI: Not stated	69%
Quist et al. (2012).	7	7	13 months	6 weeks	Aerobic and Resistance 90 mins twice weekly AI: 85-95% max HR RI: 3 sets of 5-8 reps of 70-90% 1RM	73%
Temel et al. (2009).	25	25	36 months	8 weeks	Aerobic and Resistance 90-120 mins 2 weekly AI: 70-85% max HR RI: 3 sets of 10 reps of 60-80% 1RM	A completion rate of 44%
Uster et al. (2017)	58	29	31 months	12 weeks	Aerobic, Resistance and Balance 60 mins twice weekly AI: Not stated RI: 2 sets of 10 reps of 60-80% 1RM Balance: Bilateral balance mat exercises	Mean 67% Median 75%
van den Dungen et. al (2014)	26	26	2 months	6 weeks	Aerobic and Resistance 2 hours twice weekly AI: 4 mins at 80% to 90% of	85%

					PHR alternated with 3 minutes at 50% to 70% PHR RI: 3 sets of 12 reps at 60% to 80% of 1-RM	
Zimmer et al. (2017)	30	17	10 months	8 weeks	Aerobic, Resistance and Balance 60 mins 2 weekly AI: 10 mins at 12-13 RPE RI: 2 sets of 8-12 reps of 60-80% hypothetic 1RM Balance: Balance mat work	80%

Table VI Exercise Interventions

AI: Aerobic Intensity; RI: Resistance Intensity; FI: Flexibility Intervention; HR: Heart rate; PHR: Peak Heart Rate; Mins: Minutes

3.5.3. Recruitment

Mean recruitment rate, as reported by 13 of 18 trials reviewed, was 49% (SD = 17%; range 15-74%). Patients were recruited through cancer centres, outpatient departments, palliative care and rehabilitation services. There was a positive correlation between older age and recruitment rates ($r=0.4$, $p<0.05$). Barriers to recruiting patients were systematically recorded in seven out of 18 studies (Table VI). The most common reason reported for declining participation was a lack of time. In one trial, lack of time was cited as a recruitment barrier by 50% of patients approached (Cheville *et al.*, 2010). Multiple hospital commitments were also a common reason for declining programmes. In one trial 52% of patients declined participation as it was too burdensome to get to the hospital more than once a week (Oldervoll *et al.*, 2006). In other studies, transport issues were cited as recruitment barriers, reported by 16-50% of patients approached (Cormie *et al.*, 2013b, Van Den Dungen *et al.*, 2014). Other common barriers were a lack of interest in either exercise or in participating in research generally (Temel *et al.*, 2009, Cheville *et al.*, 2010, Cormie *et al.*, 2013).

The highest recruitment rate (74%) was reported in a trial recruiting men with advanced prostate cancer, where patients were referred directly from an oncologist. Similar recruitment rates were reported in another trial in men with advanced prostate cancer, 64%, recruited directly from outpatient clinics (Bourke *et al.*, 2011). The lowest recruitment rate of all studies reviewed was 15%, where 52 out of 61 potential participants with cancer of GI origin declined to participate in a 6 week home based functional walking programme due to severe fatigue (Lowe *et al.*, 2013).

Recruitment rate did not correlate with duration of recruitment period ($r=0.13$, $p=0.3$), or with the duration of exercise programmes ($r=0.27$, $p=0.07$) (Cohen, 1992). The frequency of the exercise programmes was considered to be the number of supervised weekly exercise sessions patients were required to attend. The frequency of supervised exercise session in trials included ranged from two to three times weekly. In seven studies supervised exercise sessions were supplemented with additional unsupervised sessions that patients completed at home (Cheville *et al.*, 2010, Bourke *et al.*, 2011, Quist *et al.*, 2012, Cormie *et al.*, 2013, Lowe *et al.*, 2013, Jensen *et al.*, 2014, Chiarotto *et al.*, 2017). No correlation was found between exercise frequency and recruitment ($r=-0.38$, $p=.08$) and the number of home exercise sessions that patients were asked to complete and recruitment ($r=-.23$; $p=.48$).

Study	Number of Eligible Participants Screened	Number of Patients Recruited	Recruitment Rate	Reason for Declining Recruitment
Cheville et al. (2010).	418	115	27.5%	Extra time commitment (n=121) Low interest in research participation (n=50) Competing demands (n=37) Feeling poorly (n=34)
Cormie et al. (2013).	27	20	74%	Not interested (n=3) Health concerns (n=2) Too far to travel (n=2)
Galvão et al. (2017)	103	57	55%	Declined to Participate (n=16) Travel constraints/Proximity to Exercise Site (n=9) Other Commitments/time Constraints (n=6) GP Decline (n=5) Significant Bone Pain (n=5) Already meeting exercise oncology guidelines (n=1) No bone metastases (n=1) Unable to contact (n=3)
Hwang et al. (2012).	42	24	57%	Personal Factors (n=15) Unstable (n=3)
Jensen et al. (2014).	59	33	56%	Distance too far from home (n=12) Never been interested in sports (n=8) Too many other commitments in hospital (n=4) Other (n=2)
Oldervoll et al. (2006).	101	63	62%	Travel concerns (n=9) Already exercising (n=3) Lak of energy/mobility (n=4) Social Reasons (n=1) Did not Respond (n=11) No Reason Given (n=10)
van den Dungen et. al (2014)	60	29	48%	Travel Distance (n=17) No Interest (n=14)

Table VII Reasons Given for Declining Recruitment

3.5.4. Exercise Adherence

A level of exercise adherence was reported in all but one study (Table V); however, definitions of adherence varied widely. This heterogeneity limited the ability to examine correlates of adherence and features of exercise prescription. Levels of adherence ranged from 44% to 95%. Many studies considered patients adherent if they attended a percentage or minimum number of prescribed exercise sessions, e.g. participants were required to attend a minimum of 8 sessions (van den Dungen *et al.*, 2014); while some studies required participants to attend all sessions to be considered fully adherent (Bourke *et al.*, 2011). Alternatively, trials did not define any features of adherence

(Headley *et al.*, 2004). Adherence was also defined as the number of sessions completed over the number of sessions prescribed, giving an adherence rate of 83% (Cormie *et al.*, 2013). In contrast, a trial required participants to make up for missed days and complete 16 sessions during a 12 week period to be considered adherent. This resulted in an adherence rate of 44%, which was too low to establish the feasibility of this exercise programme (Temel *et al.*, 2009). Three studies recorded adherence to resistance training programmes (Cheville *et al.*, 2010, Cormie *et al.*, 2013, Jensen *et al.*, 2014). A two-armed trial comparing resistance and aerobic interventions reported 72% adherence to the resistance arm of a 12 week exercise intervention for gastrointestinal cancer. This was higher than the 59% adherence rate to the aerobic exercise arm of the trial (Jensen *et al.*, 2014). Adherence was defined as completion of scheduled sessions.

Four studies detailed the reasons why patients missed exercise training sessions. A total of 78% of participants with advanced cancer of mixed primary origins attended all prescribed exercise sessions (Cheville *et al.*, 2010). Reasons for missing sessions included conflicting appointments (54%), feeling too ill (31%) or too tired (8%) and patients forgetting appointments (8%). Similarly, medical appointments, travel and social commitments were listed as reasons for missed sessions in an additional trial (Galvao *et al.*, 2017). Among a group of patients receiving palliative chemotherapy, the most common reasons patients missed sessions were personal reasons (58%) or chemotherapy related symptoms such as diarrhoea (31%) or nausea/vomiting (11%) (Jensen *et al.*, 2014). A study of high intensity interval training reported that only 12.5% of participants with lung cancer attended all 24 prescribed high intensity interval training sessions however an attendance rate of 75% or higher was achieved by nine participants (69.2%) (Hwang *et al.*, 2012). Reasons for missing sessions included time limitations and family problems, as well as medical issues such as fatigue, body discomforts and falls. The absences reported by Uster et al. (2017) included sudden deterioration of health status (2 patients), non-compliance (1 patient) and treatment related complications (1 patient). No significant change occurred in adherence between the women who had progression of their disease and those who had stable or remitting disease (Headley *et al.*, 2004).

3.5.5. Attrition

The average attrition in studies included was 24% (SD = 8; Range 10-42%). Advancing disease was the most common reason for dropout from exercise interventions (Headley *et al.*, 2004, Oldervoll *et al.*, 2005b, Oldervoll *et al.*, 2006, Temel *et al.*, 2009, Cormie *et al.*, 2013b, Lowe *et al.*, 2013, Ligibel *et al.*, 2016). This included patients suffering from a decline in performance status, an increase in anti-cancer treatment and an increase in pain levels. Other reasons for dropout included family commitments and unrelated medical conditions, hospitalisation and feeling too ill and patients feeling overwhelmed (Cheville *et al.*, 2010, Bourke *et al.*, 2011, Lowe *et al.*, 2013). Four studies reported patient deaths; Jensen *et al.* (2014) reported that 4 patients died due to rapid tumour progression, while Uster et al. (2017) reported 5 deaths during a three month intervention and a further 5 deaths at the six month follow-up. Oldervoll *et al.* (2011), which was the largest study in this review, reported 10 deaths during an 8 week intervention, a total of 4.1% of the physical intervention group and 4.5% of the usual care group. Chiarotto et al. (2017) reported 15 patient deaths in an exercise intervention of indefinite duration, with patients withdrawing from the exercise programme at a mean of 164 days (95% CI 76.5–251, median 100 days) prior to their death. The highest rate of attrition (42%) was reported by Temel *et al.* (2009) in a lung cancer cohort who completed a twelve week aerobic and resistance programme. Patients were forced to withdraw from the programme due to hospitalisation (n=3), neuropathy (n=1), retinal detachment (n=1), clinical deterioration on chemotherapy (n=2) and unspecified reasons (n=1).

In the included studies, there was no correlation found between the frequency of supervised exercise sessions and programme attrition ($r=0.04$, $p=.4$). The number of home exercise sessions patients were asked to complete had no correlation with attrition rates ($r=-.21$, $p=.46$). Similarly, the duration of exercise interventions did not correlate with attrition rates ($r=0.01$, $p=.069$).

3.6. Discussion

This is the first review to comprehensively examine the involvement of patients with advanced cancer in exercise interventions. Studies included show a large variance in recruitment and attrition rates, as well as in the measurement of patient adherence to prescribed programmes. This systematic review demonstrates that there is a growing

number of studies investigating exercise programmes in patients with advanced cancer, and highlights a number of areas where the involvement of this patient group in studies involving exercise could be optimised.

Difficulties with patient accrual were reported by all studies, with one programme closing recruitment early due to slow accrual (Uster *et al.*, 2017). Factors contributing to slow accrual need to be considered as low accrual rates may lead to selection bias, thereby reducing the representativeness of this sample (Oldervoll *et al.*, 2005). Firstly, the inclusion and exclusion criteria of a number of studies included in this review may have limited the eligibility of a large number of potential patients. For example, Quist *et al.* (2012) excluded 58 participants with bone metastasis due to concerns over pathological fracture risk. Risk of pathological fracture is the most commonly reported physician concern with exercise training in patients in bone metastases (Sheill *et al.*, 2017, Sheill *et al.*, 2018), however, safe approaches to exercise prescription in patients with bone metastases have been established (Oldervoll *et al.*, 2006, Bourke *et al.*, 2011, Oldervoll *et al.*, 2011, Cormie *et al.*, 2013, Lowe *et al.*, 2013). A further, five studies excluded patients with bone metastases based on self-reported levels of pain, however two studies did not describe how pain was measured or what threshold resulted in trial exclusion. Three studies excluded patients with a resting pain >2/10 on the numerical rating scale or >3/10 on the numerical rating scale (Headley *et al.*, 2004, Oldervoll *et al.*, 2006, Oldervoll *et al.*, 2011). Another study excluded only patients with significant pain as determined by the clinician (Galvao *et al.*, 2017). Of note, pain at rest may not be indicative of fracture risk, with one study reporting that only 11% of lesions reported as mildly or moderately painful resulted in fracture, while conversely, all lesions in which pain was aggravated by function resulted in fracture (Fidler, 1981). Pain, particularly pain associated with function, could be used as a criterion which would exclude only those patients at high risk of pathological fracture from participating in exercise programmes (Sheill *et al.,* 2018). Some of the most recent studies in advanced cancer have included patients with bone metastases, or excluded only patients with moderate to severe bone pain which limited activities of daily living or those with acute fracture risk (Cormie *et al.*, 2013, van den Dungen *et al.*, 2014, Ligibel *et al.*, 2016, Zimmer *et al.*, 2018). This is encouraging, as the exclusion of patients with bone metastases may result in a greater decline in musculoskeletal structure and function and deny patients the opportunity to make gains in muscle strength and aerobic capacity which are associated with structured targeted exercise programmes (Cormie *et al.*, 2013). A recent study suggested that in mice models, mechanical loading inhibits the growth and osteolytic capability of secondary breast tumours after their homing to the bone (Lynch *et al.*, 2013). This

potential benefit of weight bearing exercise now needs further investigation in patients with advanced disease. Broadening inclusion criteria to include patients with skeletal metastases is an integral part of this change.

The inclusion of a clinical estimate of prognosis may also reduce the eligibility of many patients for exercise trials. Studies with the highest recruitment rates in this review did not limit the life expectancy of patients in inclusion criteria (Bourke *et al.*, 2011, Bourke *et al.*, 2014) or outlined wide acceptable margins of 3 months to 2 years (Oldervoll *et al.*, 2006, Oldervoll *et al.*, 2011, Cormie *et al.*, 2013). In contrast, Cheville *et al.* (2010) limited inclusion to both life expectancy and 5 year survival rates resulting in a recruitment rate of 27.5% in patients with GI primary tumours. Oldervoll *et al*., who listed no exclusion criteria and included all patients with incurable disease and adequate pain control, recruited the highest number of participants of all the studies reviewed (n=232) (Oldervoll *et al.*, 2011). Exercise trials involving patients with advanced cancer appear to face many of the same recruitment challenges as trials recruiting patients at an earlier stage of disease. Reported recruitment rates varied widely among the studies reviewed, similar to studies in early stage cancer patients or cancer survivors (Irwin *et al.*, 2008, Penttinen *et al.*, 2009). With increasing evidence supporting the safety and efficacy of exercise training in those with complex advanced cancers, increasing the eligibility criteria for exercise interventions may improve accrual numbers of patients with advanced cancer to exercise trials. Exercise interventions should to aim to accommodate patients regardless of life expectancy and with multi-morbidities related to both cancer and advancing age. This would reflect the complex presentations of these patients in the clinical environment.

Definitions and the measurement of exercise adherence varied widely. Many studies reviewed considered adherence solely as patient attendance at exercise sessions and not the level of activity completed at these sessions. This may have resulted in 'adherent' patients not completing the exercise programmes in full. Studies should complete a multi-factorial assessment of adherence in order to accurately determine the treatment effects of exercise, as in the study by Cormie *et al.* (2013), which considered adherence in terms of both the number of session's patients completed and also the amount of sessions completed in accordance with exercise prescribed. This method provides a means of capturing any deviations from the programme, e.g. patients not fully completing exercise sets or attending sessions but not exercising. Unfortunately the study by Cormie *et al.* (2013) was the only study reviewed to monitor exercise in such a detailed capacity. The variety of exercise adherence definitions used, make it difficult to draw

commonalities or conclusions from results found. Common assessment methods for exercise adherence include subjective measurements such as self-report inventories and exercise logs, objective measurements such as accelerometers and heart rate monitors, and observational measurements (Adams *et al.*, 2015). In this review, assessments included only exercise logs and class attendance (Bourke *et al.*, 2011, Bourke *et al.*, 2014). Alternative methods of measuring adherence such as heart rate monitors and mobile phone apps have been used previously in trials involving cancer patients (Walsh *et al.*, 2010) and may have a role in adherence monitoring in future exercise trials to ensure patients follow the parameters of prescribed exercise sessions correctly.

Exercise training parameters were inconsistently measured and lacked standardisation, making it difficult to ascertain the relationship between programme structure and participant engagement. Standardised outcome sets, which outline a minimum sufficient set of outcomes for important medical conditions, should be used in order to increase the pool of comparable data in studies examining similar interventions in a cancer cohort (Comet Initiative, 2013). In particular, consensus is required on the measurement of exercise intensity and, as previously mentioned, patient adherence. Aspects of exercise programme structure such as the duration and frequency of the exercise intervention did not appear to impact recruitment, retention or adherence of participants, suggesting that other aspects of study design should be explored to further explain the large variance in these rates in an advanced cancer population. Knowledge about the type of physical exercise most beneficial for patients at different stages of disease progression is still lacking. Not all persons with metastatic or advanced cancer are in the palliative or end-of-life phase and many have a great need to maintain their functional capacity. Future exercise interventions in this population should monitor the adherence of these participants closely using standardised definitions and objective measurements where possible in order to determine the dose/response effect of exercise in this population (Li *et al.*, 2015). While the exercise interventions included in these studies were tolerated well by participants, a number of barriers remain to recruiting patients to these exercise programmes. Concentrated efforts are now needed to reduce these barriers.

3.7. Strengths and Limitations

A strength of the review is the identification of key areas which need to be addressed in future trials, such as the definition of key outcomes and potential ways to optimise trial

recruitment. The database EMABASE was not searched, which is a limitation of the current study. Due to the small number of studies, the heterogeneity in populations and definitions of key variables the discussion of trends in outcomes was extremely limited. There is a possibility that some studies that included patients with advanced cancer were not included here as a number of studies screened did not detail the cancer stage of participants. E-mails were sent to corresponding authors to clarify this; however, if there was no response then studies were then excluded.

3.8. Conclusion

Participant recruitment and adherence rates varied considerably among the studies reviewed and there were inconsistencies in how adherence to programmes were measured. With increasing evidence supporting the safety and efficacy of exercise training in patient with advanced and complex presentations, broadening the inclusion criteria of exercise trials to increase the number of advanced cancer patients who are eligible for physical activity interventions will increase recruitment rates and ensure those patients recruited represent the advanced cancer population found daily in clinical practice.

4. Chapter 4: The Views of Patients with Metastatic Prostate Cancer towards Physical Activity: A Qualitative Exploration

4.1. Introduction

The following chapter explores the attitudes of patients living with metastatic prostate cancer towards physical activity. This study has been published in *Supportive Care in Cancer (Sheill G., Guinan, E., Neill, L.O. et al. Support Care Cancer (2017)* https://doi.org/10.1007/s00520-017-4008-x (Appendix 4)).

As described in Chapter 1, patients with metastatic cancer can experience debilitating symptoms, such as pain, breathlessness, fatigue and nausea; which may influence attitudes towards, and engagement in physical activity. However, Chapters 1 and 3 describe how individually prescribed physical activity programmes can be safely introduced for patients with many symptoms of advanced disease, including bone metastases (Oldervoll *et al.*, 2011, Cormie *et al.*, 2013, Bourke *et al.*, 2014). Increasing physical activity levels can improve measures of physical performance and quality of life (QoL) for this patient cohort (Beaton *et al.*, 2009). When patients are not able to undertake moderate and/or vigorous activities, even low-intensity physical activity after a cancer diagnosis is associated with improved outcomes (Holmes *et al.*, 2005, Kenfield *et al.*, 2011). However, men with metastatic prostate cancer who do not meet aerobic exercise guidelines have been shown to have significantly lower physical functioning, role functioning (physical and emotional) and general health scores than men who met the guidelines (Zopf *et al.*, 2017).

Over 90% of patients with advanced cancer are interested in completing physical activity programmes (Lowe *et al.*, 2010). However; many patients living with bone metastases become inactive due to the side effects of cancer and its associated treatments, or the fear of skeletal fracture (Coleman, 2006). One study involving 55 patients with metastatic prostate cancer objectively measured physical activity levels demonstrated only 29% of participants met the current aerobic exercise guidelines for cancer survivors while 71% were insufficiently active (Zopf *et al.*, 2017). It is essential to make exercise interventions accessible and adaptable to patients living with metastatic cancer, in order to ensure the number of patients obtaining the physical and psychological benefits associated with physical activity is maximised. Additionally, it is important to identify the factors which may play a role in the illness experience of metastatic cancer patients and that may contribute to physical inactivity. Future physical activity interventions may then consider

this knowledge in order to meet the specific exercise needs and capabilities of patients with metastatic prostate cancer.

4.2. Study Aims and Objectives

The overall aim of this study was to qualitatively explore the views of men diagnosed with metastatic prostate cancer towards physical activity. The specific objectives of the study were:

- To explore participants' perceptions about their own physical activity.
- To describe the effect of an advanced cancer diagnosis and associated treatment on participants' physical activity levels.
- To identify potential barriers and facilitators to engaging in physical activity.

4.3. Materials and Methods

4.3.1. Study design

A qualitative study design was used in this study and individual semi-structured interviews with open-ended questions took place. The attributes of qualitative research and the research approach taken are described in Chapter 2 (Section 2.1.1 & Section 2.2.1).

4.3.2. Participants and Procedures

Patients with metastatic prostate cancer, who were recruited to the ExPeCT randomised control trial (Clinicaltrials.gov NLM Identifier: NCT02453139), presented in Chapter 6, examining the effect of exercise on circulating tumour cells were eligible to complete interviews for the present study. Metastatic cancer (also known as advanced or palliative) includes the American Joint-Committee on Cancer definition of Stage IV cancer (Edge and Compton, 2010). Patients were recruited from oncology clinics at three hospital sites. Inclusion criteria for the randomised control trial are: patients ≥ 18 years and male, a histologically confirmed diagnosis of prostate adenocarcinoma, metastatic disease as confirmed by CT/MRI or by bone scan, stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to recruitment and capable of participating safely in exercise.

Exclusion criteria included a history of radical prostatectomy and a previous diagnosis of any other malignant tumour.

The Health Belief Model (HBM) guided the development of interview questions. The HBM framework has been widely accepted as an organising framework which predicts health behaviours by focusing on the attitudes and beliefs of individuals (Janz and Becker, 1984). For example, participants were asked “What factors, if any, do you think prevent you from engaging in or increasing your physical activity since your cancer diagnosis?”. This question was developed to determine barriers to physical activity post-diagnosis. Examples of questions in the interview guide are included in Table VII.

Interview Question Topic	Example Question
Self-Efficacy	Do you feel you could complete as much physical activity as your peers?
Benefits to physical activity participation	What makes you want to be physically active?
Barriers to physical activity participation	What factors, if any, do you think prevent you from engaging in or increasing your physical activity since your cancer diagnosis?
Cues to Action	How do your family feel about you participating in regular physical activity?

Table VIII Example questions from the interview guide

4.3.3. Data Collection

Interviews took place in either the Clinical Research Facility, St. James’s Hospital or the Physiotherapy Department, Tallaght Hospital. The first 20 patients recruited to a clinical trial were invited to complete qualitative interviews prior to patient randomisation. Data saturation was used as a guiding principal for sample size, which was determined iteratively. Age, body mass index, waist circumference and burden of metastatic disease were recorded for each participant as part of their baseline Randomised Controlled Trial assessment. Participants also completed a self-report physical activity questionnaire (Physicians’ Health Study Assessment). Participants were interviewed using audio recorded, face-to-face, semi-structured interview format. Each interview lasted between

15 to 20 minutes and was recorded using a digital voice recorder (Philips Voice Tracer digital recorder 3400). I completed interviews with all participants involved in this study.

Topics and issues to be explored and discussed were specified in advance and an interview guide was created to lead the interview process. The order and sequence of the questions was decided by the researcher. During the interview, participants were probed for detail and the interviewer developed the questions. Because semi-structured interviews remain conversational and situational, gaps in data can be explored and closed. Interview questions were open ended, to provide more exploratory, developmental and contextual data (Blessing and Forister, 2012).

4.3.4. Data Analysis

All interviews were tape-recorded and transcribed verbatim. Having the researcher transcribe the data offers the best chance that the content, punctuation and tone of the interview are reflected in the transcript and allows the researcher to become thoroughly familiar with the data (Carpenter and Suto, 2008). In line with data confidentiality procedures, each participant was assigned a study code on completion of the interview. All names and any other details that could possibly identify participants were removed from the transcripts.

Transcripts were analysed using content analysis (Hsieh and Shannon, 2005). The seven steps of content analysis are outlined in Table VIII. Both thematic analysis and content analysis approaches would have been suitable for use in this thesis. Thematic analysis, as described by Braun and Clarke, was not chosen as it was thought that content analysis, as described by Hsieh and Shannon, would allow the research to choose either developing themes or categories – compared to thematic analysis which requires the researcher to consider both. Although thematic analysis can provide a rich and detailed, yet complex, account of the data, content analysis was also chosen for this thesis as it involved conducting exploratory work in an area where not much is known. Content analysis was suitable for the simple reporting of the common issues mentioned in data (Green & Thorogood, 2004).

Two researchers read each interview script independently. Transcripts were analysed line by line for themes reflecting factors affecting physical activity in men with metastatic prostate cancer. Comparative analysis was conducted with subsequent transcripts to build findings upon themes that had previously emerged. Themes were first subject to broad inclusion so as not to restrict the validity of the data due to premature categorisation. As further interviews were analysed, responses were grouped first into sub-themes. These emergent themes were used to organize and group categories into meaningful clusters (Coffey & Atkinson, 1996; Patton, 2002). This larger number of subcategories into a smaller number of categories. These were compared, discussed and organised by the same researchers. Data saturation was reached by interview 17. The remaining three interviews were used to confirm and clarify the analysis. Demographic data were entered into an Excel database and analysed descriptively.

1	Formulating the research question
2	Selecting of sample and unit(s) of analysis
3	Defining the categories
4	Outlining the coding process
5	Implementing the coding process
6	Determining trustworthiness
7	Analysing and representing the results

Table IX Seven Steps of Content Analysis

4.3.5. Ethical Approval

Ethical approval was granted by St. James's Hospital/Adelaide Meath National Children's Hospital research ethics committee and all participants provided written informed consent to complete interviews.

4.4. Results

Twenty patient interviews were completed. All patients who were invited to participate consented to interview. Participant demographics and clinical characteristics are described in TableIX.

	Total
Age (mean ± SD) years	71 (SD 8.5)
BMI (mean± SD) Kg/m^2	30.19 (SD 5.37)
Waist Circumference (cm ± SD)	104±15.2
Time Since Cancer Diagnosis (Months, median (IQR))	10.5 (6.25-22.25)
Severity of Bone Metastatic Disease n (%)	
Minor (1 region affected)	5 (25)
Moderate (2 regions affected)	4 (20)
Major (>2 regions affected)	11 (55)
Primary treatment n (%)	
Radiation therapy	5 (25%)
Hormones	19 (95%)
Achieving Aerobic Physical Activity Guidelines (%)	
Yes	9 (45)
No	11 (55)
Physical Activity Category	
Light (MET-h/wk value < 3)	10 (50%)
Moderate (MET –h/wk between 3-5.9)	9 (45%)
Vigorous activities (MET-h/wk value of_≥6)	1 (5%)

Table X Participant Characteristics

SD: Standard Deviation, MET: Metabolic Equivalent, h/wk: Hours per week

The results of the content analysis were classified into four major themes (Table X). A mind-map of emergent themes is shown in Figure 19. Quotations reflecting the range of issues that emerged are presented and were selected because they were typical of the insights that participants gave during interviews.

Major Themes	Sub-theme
Barriers to physical activity	Physical Barriers Psychological Barriers Environmental Barriers
Benefits of physical activity	Weight Loss Increased Energy General feeling of well-being
Reduction in physical activity levels post diagnosis	A disruption to normal daily routine Patients unable to overcome barriers to physical activity
Social support for physical activity	Differences in the level of family support for physical activity Different perceptions of physical activity levels of peers

Table XI Qualitative Themes Identified

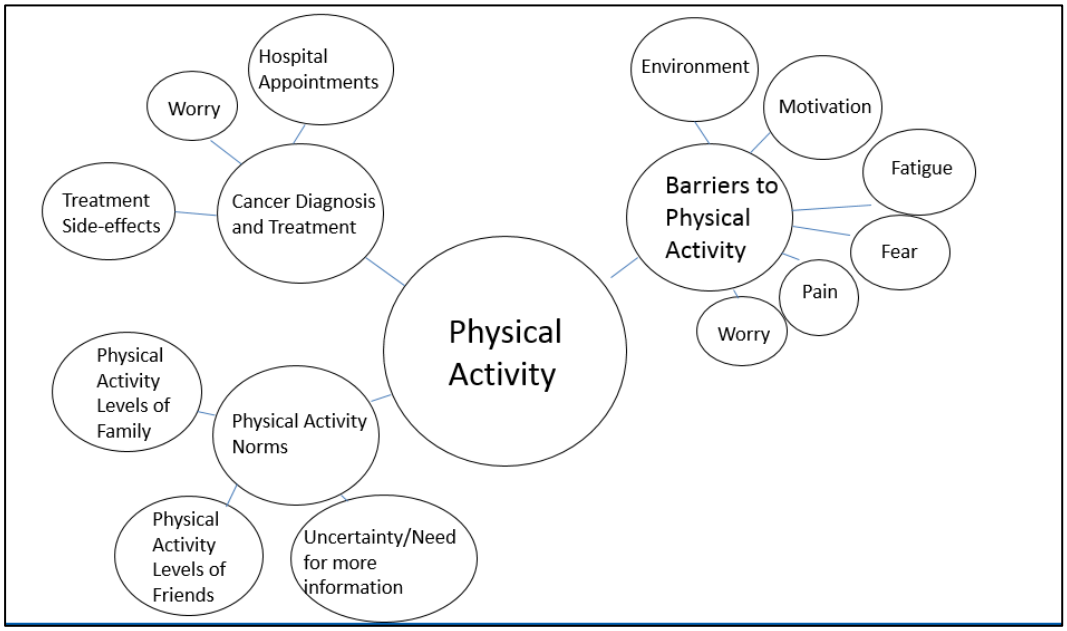


Figure 19 Thematic mind-map

4.4.1. Barriers to Physical Activity

Exercise barriers were mainly related to metastatic cancer and the side effects of cancer treatment including hormone therapy and chemotherapy. Additionally, physical, psychological and environmental barriers to physical activity were mentioned.

Many patients reported that the symptoms of metastatic disease which they were experiencing were acting as barriers to engaging in physical activity.
"It was that pain along the bottom of my back that was really stopping me a lot" (P 02),

"I think it was the pains that were obviously beginning to come from the cancer" (P 04).

Fatigue also made it difficult for patients to increase their physical activity.
"It's difficult when you're feeling tired. I get awful tired. Awful tired those damn hormones" (P 11)
"I find that I get very tired if I try to do exercise" (P 04)

"The chemo was the turning point. No energy. I would walk around the corner with the dog and I would be flat." (P 14)

Other factors such as low mood and low confidence were also reported by patients;
"Those hormones. And you know you feel very down with them" (P 11)

"I'll make a fool of myself but no…..I'd say that I won't be able to…" (P 05)

Issues around urinary incontinence were also identified as barriers to exercise;
"It's quite embarrassing actually you would be out playing badminton and the next minute you would have to run to the toilet" (P 10)

"I have to go straight away. Sometimes I control a little but I have to go straight away." (P 14)

Additionally, the effects of hormone treatment during exercise were mentioned;
"The hot flushes...they vary in terms of intensity. When I get the hot flushes I feel this thing going right up through my body. Pin pricks right up through my body." (P 14)

Bad weather was mentioned by many as a barrier to exercise;
"*I hate the weather and I thought of joining the gym locally instead but that's not as good as being out on the road for me" (P 01)*

"I haven't been doing anything because of the bad weather' (P 07)

"I don't feel very comfortable walking in the cold." (P 13)

A lack of suitable facilities for exercising due to rural living was also a barrier,

"*You have to drive to town to do it because there is no footpaths on the roads and it's too dangerous." (P 10),*

"I try but I'm out in the country" (P 11)

Low motivation was another reason for poor physical activity levels;
"I reckon my enthusiasm has gone down to some extent" (P 01)

"I think I should get more done, I should walk more" (P 04)

"It's hard to motivate yourself to get up and get going" (P 10)

Finally, difficulties exercising independently were also identified;

"*If someone else was doing it I would do it you know that sort of way. If I do it on my own you know…..it's not the best." (P 18)*

4.4.2. Benefits of Physical Activity

When asked about the benefits of physical activity, the majority of patients referred to the general health benefits of physical activity;
"*It would make me more fitter and it would be something I would look forward to I imagine" (P 016)*

"You just feel so much better" (P 019)

There was a sense that physical activity facilitated participants to regain a routine and normality
"*I would like to be able to get back to what I was doing before" (P 02)*

Only a small number of the specific health benefits of exercise were reported. Weight loss was most commonly reported, followed by an increase in energy levels. Others referred to benefits of exercise unrelated to physical health;
"*It keeps me busy*" (P 09)

Patients reported few specific benefits of exercise related to a cancer diagnosis. Walking, swimming and cycling were the modes of exercise participants felt were of most benefit;
"Maybe a bit of walking…..anything to get the heart pumping." (P 16)

4.4.3. Reduction in Physical Activity Levels Post-diagnosis

Many patients reported a history of being active, both in their childhood and as an adult prior to their cancer diagnosis. Many patients reported high physical activity levels in the past due to jobs in areas such as farming or the armed forces and from walking or cycling to and from work. Other participants were active mainly for leisure;
"Well, I played hockey, field hockey until I was 52 and I played hurling and gaelic football when I was young and I played a lot of tennis" (P 04).

Several patients commented on a recent change in physical activity levels and a significant number described a decrease in physical activity levels after being diagnosed with advanced cancer;
"I used to be very fit…but that's water under the bridge" (P 15)

"*Before I got this diagnosis of the cancer I was walking"* (P 08)

"*I played badminton actually until February last year*" (P 10)

Patients describe a decrease in physical activity levels after their diagnosis for many reasons and attributed this to issues such as the high number of hospital commitments following diagnosis and the disruption a cancer diagnosis brought to normal routines.
"I started getting hospital appointments and all that kind of stuff and it put me onto a different cycle and I stopped doing the regular exercise" (P 01)

"It was just then when I stopped that I never got back to it" (P 05)

Some were unsure of the effects of exercise post-diagnosis and reported feeling unsure about what physical activity to undertake
"*I didn't know whether to exercise or not.*" (P 02)

"What are you to say when you have a cancer that has gone into the skeleton? You just don't know. You just keep going as best you can" (P 04)

4.4.4. Social Support for Physical Activity

There was a large variation across the study sample in levels of support from family and friends in relation to physical activity. When asked about family attitudes towards their physical activity, half of participants reported their family are very supportive;
"They encourage me, like to see me up and about" (P 03)

"They want me to do it" (P 05)

''They don't want me lying in bed. They want me to be up going around." (P 06)

"They say it to me as well ….you're not out on the farm, you have to keep moving….. They would like to see me doing something" (P 11)

In contrast, other participants felt family were indifferent to what physical activity they completed, while others were unsure about their family's feelings on the matter.
"They would leave it up to myself." (P 02),

"I think they would be very uninterested…." (P 01)

"They don't care what I do" (P 06), "They don't mind what I do" (P 08)

"They are happy enough…they don't like to see me on my bike though. Sometimes they say you're too old…….not for me. I don't think so" (P 09)

No patients mentioned that a diagnosis of metastatic prostate cancer as an issue of concern for family members in relation to physical activity.

The majority of patients felt they were less active than their peers or felt that the level of physical activity which they engaged with wasn't enough. In general, participants were unsure how their physical activity levels compared with others;
"I think at the present I would be behind a fair bit" (P 08)

"It's hard for me to know about what I do. I don't really have a bench mark to sort of measure it. I'd say ……. I'm not too bad" (P 04)

Of interest, one patient perceived themselves to be as active as their peers.
"*I'm normal, I'm exercising as much as anybody else" (P 03)*

Many patients commented on how they had no way of knowing what exercise or how much exercise others completed;
"*I don't know what anyone else is doing" (P 10)*

"I don't see anyone else" (P 11)

4.5. Discussion

The purpose of this study was to determine the perceptions of men with metastatic prostate cancer towards physical activity. This study outlines generic and cancer specific barriers to physical activity perceived by patients with metastatic prostate cancer. Patients associated the time following a diagnosis of advanced cancer with a decline in physical activity levels. Patients had limited knowledge of the health benefits of physical

activity, highlighting the need to increase education around physical activity post diagnosis.

Many participants in this study reported a decrease in physical activity levels following a diagnosis of advanced prostate cancer. This is similar to findings in previous studies of patients with early stage breast and colorectal cancer (Irwin *et al.*, 2003, Meyerhardt *et al.*, 2006). Patients in this study offered potential explanations for this decline in physical activity levels including the disruption to daily routines caused by multiple hospital visits and the side effects of cancer treatment. These findings are similar to those in previous studies, where an association between common treatments for the management of bone metastases, such as radiation therapy and chemotherapy were found (Dahele *et al.*, 2007, Ferriolli *et al.*, 2012). There is however a growing body of literature examining the benefits of maintaining and increasing physical activity levels during cancer treatment, including chemotherapy, radiation therapy and hormone therapy (Mock *et al.*, 1997, Segal *et al.*, 2009, Swenson *et al.*, 2010, van Waart *et al.*, 2015, Moyad *et al.*, 2016). Efforts are needed to increase physical activity levels of patients after diagnosis and during the treatment stage of advanced cancer. These could include patient education around the importance of physical activity during this time, and the provision of exercise information leaflets, verbal advice or the referral of patients to appropriate exercise services. Previous studies in breast cancer populations have shown even the provision of standard public health physical activity recommendations to patients post-cancer diagnosis can have long-term effects on physical activity engagement (Jones *et al.*, 2004, Vallance *et al.*, 2008).

Study participants reported many barriers to engaging in physical activity. A number of these barriers are similar to those reported in studies of patients with early stage disease and indeed the general population, e.g. difficulty accessing exercise facilities and bad weather (Hefferon *et al.*, 2013), initiating and maintaining a regular exercise regimen (Ng *et al.*, 2012), however participants in this study also described many physical and psychological side effects of metastatic prostate cancer as barriers to engaging in physical activity. The spread of cancer into the bones was a cause of concern for some, leading to uncertainty about the role of exercise. An additional worry centred on problems relating to exercising with poor urinary and bowel control, common in men diagnosed with prostate cancer (Glaser *et al.*, 2013). These complex presentations reflect why individuals with a cancer diagnosis are considered a special population in terms of exercise prescription (Hayes *et al.*, 2009). Physical activity barriers have proven to be predictors of exercise behaviour (Ellis *et al.*, 2013) and so each patient reported

barrier needs to be examined and addressed carefully in order to optimise the engagement of patients with metastatic cancer in physical activity.

Additionally, adverse symptoms of long-term hormone treatment were highlighted, such as weight gain and fatigue (Galvao *et al.*, 2007). Difficulties with weight management while on hormone treatment, reported by participants in this study, may have contributed to the high BMI of participants. Engaging in physical activity which involves resistance and cardiovascular exercise has been shown to have beneficial effects on both fatigue (Segal *et al.*, 2003) and body composition (Galvao *et al.*, 2006) for men on hormone treatment. The uncertainty reported by patients regarding the type and duration of physical activity suitable for patients with a diagnosis of metastatic cancer further highlights the need for patient education in this area. Patients may benefit from referral to appropriate exercise therapists specialised in the area of oncology to discuss physical activity plans during cancer treatment and recovery. Exercise prescription by a specialist with oncology specific education and training is a preference identified by many patients with cancer (Karvinen *et al.*, 2006, Jones *et al.*, 2007), and will ensure patients with metastatic cancer receive appropriate and achievable exercise plans which consider the relevant physical and psychological side-effects of their stage of cancer and cancer treatment (Hwang *et al.*, 2008).

Participants in this study described a large variation in their perceived level of family support for physical activity ranging from very supportive to indifferent. A previous study of patients with brain metastases found that despite having full ambulation 49% of patients preferred completing their physical activity with a spouse, caregiver, family or friend. This suggests a patient need for emotional, rather than physical, support from people close to them (Lowe *et al.*, 2016). A number of patients in the current study commented on the indifference of family members regarding their physical activity levels. Often families may not discuss physical activity with patients as they feel a need to support the patient's autonomy and also due to the expectation of negative and defensive reactions to suggestions regarding initiating or increasing exercise behaviour (Rhudy *et al.*, 2015). In a review examining the correlates of adults' participation in physical activity, all studies that included a measure of social support for physical activity found a significant positive association with physical activity (Trost *et al.*, 2002). For patients diagnosed with cancer, social support may affect attitudes and normative beliefs about the impact of lifestyle changes on their treatment outcomes (Coleman *et al.*, 2014). The importance and value of physical activity for patients with metastatic cancer should be discussed with patients' family members. Physical activity consultations for patients

diagnosed with cancer may have a role in assisting patients and families to overcome interpersonal issues. Exercise specialists treating patients with metastatic cancer should consider the role of family support when prescribing physical activity programmes to patients.

4.6. Clinical Implications

This study outlined many physical activity barriers associated with suboptimal activity levels in patients diagnosed with metastatic prostate cancer. Physical activity in patients with metastatic cancer should be encouraged in clinical practice. When symptoms of metastatic prostate cancer are reported as barriers to engaging in physical activity, patients should be referred to the appropriate healthcare professionals for the assessment and management of these symptoms and for guidance on how to exercise according to symptom severity.

4.7. Study Limitations

All participants in this study had agreed to participate in a randomised control clinical trial involving a physical activity intervention which introduces a substantial self-selection bias and limits the applicability of study findings to all men with metastatic prostate cancer. While this study demonstrated that there are patients with metastatic prostate cancer with a high disease load willing to participate in physical activity interventions, further research is required to explore the issues identified within this study within the wider metastatic cancer population.

4.8. Conclusion

The results of this study demonstrate that men living with metastatic prostate cancer have unique needs regarding physical activity related to symptoms of both their cancer and cancer treatment. There is a need to increase prompts that encourage patients with metastatic cancer to maintain/increase their physical activity levels post-diagnosis. Given the individualised needs of this patient group, referral to a cancer exercise specialist should be considered for the prescription of tailored physical activity programmes.

5. Chapter 5a: Physical activity and advanced cancer: The views of chartered physiotherapists in Ireland

5.1. Introduction

The following chapter explores the views of healthcare professionals towards physical activity in patients with advanced cancer, including those with metastatic disease. The work presented in this chapter has been published in the peer-reviewed journal Physiotherapy Theory and Practice (Gráinne Sheill, Emer Guinan, Linda O Neill, David Hevey & Juliette Hussey (2018): Physical activity and advanced cancer: The views of chartered physiotherapists in Ireland DOI: 10.1080/09593985.2017.1422821) (Appendix 5).

Consistent evidence supports a role for exercise training and physical activity during and after cancer treatment to enhance physical performance, reduce fatigue levels and improve quality of life (Dimeo *et al.*, 1997, Courneya *et al.*, 2003, Dimeo *et al.*, 2003). Despite this, physical activity participation declines substantially during treatment (Eyigor and Kanyilmaz, 2014) and physical activity levels among cancer survivors are below recommended levels (Lynch, 2010, Guinan *et al.*, 2013). As described in Chapter 1 and Chapter 3, this is a particularly pertinent issue in the advanced cancer population as physical functioning and physical condition are among the most important determinants of palliative patients' quality of life (QoL) (Oldervoll *et al.*, 2006). Improved treatment options allow patients to live with advanced or metastatic cancer for longer; however, many patients remain inactive due to the side effects of cancer and its associated treatments (Coleman, 2006). Physical symptoms such as pain, breathlessness, fatigue and oedema are especially common and occur in some combination in virtually all patients with advanced cancer (Solano *et al.*, 2006). Pain, depression, and fatigue are a symptom cluster associated with reduced physical functioning (Laird *et al.*, 2011). Despite this, studies have also shown that exercise training is safe during and after cancer treatment (Brown *et al.*, 2003, Knols *et al.*, 2005, Schmitz *et al.*, 2010) and systematic reviews have determined that both resistance and aerobic activity programmes are both safe and beneficial for patients with metastatic disease (Beaton *et al.*, 2009, Albrecht and Taylor, 2012). Additionally, patients with a life expectancy of <1 year are willing and able to attend physical activity programmes (Oldervoll *et al.*, 2005). Physiotherapists, also known globally as physical therapists, work closely with patients to alleviate the physical side effects of cancer and its treatment, and encourage physical activity. Physiotherapy involvement in the later and terminal stages of disease can

enable patients to improve QoL, as physiotherapists use their knowledge and skills to highlight the importance of physical activity in the management and reduction of cancer related side effects (Okamura, 2011). To date, there are no exercise guidelines specifically for patients with advanced or metastatic cancer. It is recommended that all patients with cancer (receiving treatment, following treatment, curative and palliative) complete 150 minutes/week moderate-intensity aerobic exercise or 75 minutes/week of vigorous exercise, as prescribed for a healthy population (Thompson *et al.*, 2013). However, due to the complex symptoms of an advanced state of disease, many patients with metastatic disease require tailored exercise guidance (Cormie *et al.*, 2013). For example, patients with bone metastasis require exercise programmes that consider the level of morbidity associated with the location and type of their metastatic lesion. As a consequence of their individual needs, many patients seek out, or are referred to physiotherapists for physical activity recommendations and guidance.

Physiotherapists make physical activity recommendations and guide patients through cancer rehabilitation programmes based on their clinical knowledge and the best available evidence (Wolin *et al.*, 2012). The lack of specific guidelines regarding exercise prescription for patients with advanced cancer is noticeable and may have implications for chartered physiotherapists practicing in this area in Ireland and further afield. Prescribing exercise and physical activity to patients with advanced cancer in both inpatient and outpatient settings may present many challenges to therapists due to the complexity of this disease presentation and the concurrent pharmaceutical management. The views held by physiotherapists have previously shown an association with clinical practice behaviour (Bishop *et al.*, 2008). The Health Belief Model (HBM) is a framework that may be used to explore the views of physiotherapist in order to gain a greater understanding of the current clinical practice around prescribing physical activity to patients with advanced cancer. The HBM suggests that a set of attitudes or beliefs lead to behaviour (Janz and Becker, 1984). This study will use the constructs of the HBM to examine physiotherapists' views of physical activity, including its benefits and barriers, for the advanced cancer population. Physiotherapists' self-efficacy around prescribing physical activity to this patient group will be examined, as well as any perceived cues to action or activation strategies which may trigger increased physical activity levels in this patient population (Rosenstock and Hochbaum, 1961, Deo *et al.*, 2013).

5.2. Study Aims and Objectives

The overall aim of this study was to explore physiotherapists' views of physical activity for patients with advanced cancer. The specific objectives of the study were:

a) To describe Irish chartered physiotherapists' views on the role of physical activity for patients with advanced cancer.
b) To explore physiotherapists' prescription of physical activity for two case studies of patients with advanced cancer.

5.3. Materials and Methods

5.3.1. Study design

This study used a mixed methods study design, involving both quantitative and qualitative questions as discussed in Chapter 2 (Section 2.1.1 & Section 2.2.1).

5.3.2. Participants

A link to an online questionnaire and participant information leaflet were sent to the physiotherapy managers of the eight designated cancer centres in Ireland (Four in Dublin, and one in each of Cork, Galway, Limerick and Waterford) for distribution to all physiotherapists working in these centres. The Irish Society for Chartered Physiotherapists' office also distributed the survey among the national clinical interest groups for Chartered Physiotherapists in Oncology and Palliative Care (n=55) and Chartered Physiotherapists in the Community (n=113). Only physiotherapists treating patients with advanced cancer were asked to complete the online survey. The study protocol was approved by the Trinity College Faculty of Health Sciences Ethics Committee (Ref: 20150609).

5.3.3. Study Instrument

Using an online survey service (via SurveyMonkeyTM, SurveyMonkey.com, LLC, Palo Alto, CA, USA) an anonymous questionnaire was created. The survey included demographic questions; 10 attitude questions based on the guiding principles of the Health Belief Model (Janz and Becker, 1984), and two case study questions.

Demographic information was collected relating to the physiotherapist's job title, years of experience and place of work. Physiotherapists' views of prescribing physical activity to this population were assessed by 10 statements rated on a 7-point Likert scale, ranging from 'strongly agree' to 'strongly disagree'. The items assessed included statements on the benefits and safety of exercise for this population.

The survey also included two patient case studies. These case studies were specifically designed by the research team to represent typical advanced cancer patients referred for outpatient physiotherapy in a national clinical centre.

Case Study 1:
Patient 1 is 86 years old with widespread axial metastases secondary to prostate cancer. He has few co-morbidities and has been active all his life. During his consultation he mentions to you that he plans on remaining active and continuing activities, which include manual labour in the garden and playing golf every day.

Case Study 2:
Patient 2 has stage IV prostate cancer with bone metastases to his proximal femur and pelvis. He has a poor relationship with physical activity and multiple co-morbidities. He feels that his diagnosis with cancer is another reason to limit his physical activity.

Physiotherapists were asked to provide physical activity recommendations for patients, as well as outline any concerns they had relating to physical activity in the cases provided. Responses were open ended. All response data was stored on a password accessed server and the survey was live for a six week period.

5.3.4. Analysis

Data was exported to SPSS for analyses. Physiotherapists' views towards recommending exercise were analysed using descriptive statistics. Text-based responses to open-ended questions related to the case studies were analysed using content analysis (Hsieh and Shannon, 2005). In accordance with the aims of the study, analysis focused on physical activity recommendations and concerns around physical activity. The author read a document comprising all participant responses several times to permit familiarisation with the data and to identify initial patterns. An initial coding scheme was developed after the first ten responses that guided the coding of all

remaining responses. Codes were then sorted into emerging categories based on relations between codes and then summarised into emerging themes. To increase the rigour of the analysis, a second author (LON) analysed all responses independently and combined results with the first author. There were very high levels of agreement in the coding of categories between the two researchers, with no instances of significant disagreement.

5.4. Results

5.4.1. Physiotherapists' Information

A total of 38 physiotherapists responded to the survey (Table XI). Of this, the majority of physiotherapists were senior physiotherapists (physiotherapists holding a minimum of three years' post-qualification clinical experience), followed by basic grade or entry level physiotherapists. A small proportion of respondents were clinical specialists (physiotherapists holding a minimum of five years' post-qualification clinical experience and a postgraduate qualification relevant to the post) or managers. The majority of physiotherapists were qualified between 10 and 20 years (n=16 (42%)) or over 20 years (n=11 (29%)) followed by therapists qualified between 5-10 years (n=6 (16%)) or less than 5 years (n=5 (13%)).

Physiotherapy Grade	**Number of respondents (Percentage)**
Basic Grade	8 (21%)
Senior	25 (65%)
Clinical Specialists	2 (6%)
Managers	3 (8%)
Area of Work	
Hospital Setting	13 (34%)
Community Setting	20 (53%)
Private Practice	1 (3%)
Hospice Care	4 (10%)

Table XII Participant Characteristics

5.4.2. Physiotherapists' views towards physical activity

The vast majority of physiotherapists agreed with the statement "being physically active is important for patients with advanced cancer" (94%, Table XII). Additionally, a high proportion of physiotherapists agreed that patients with advanced cancer are capable of completing physical activity programmes and also reported prescribing physical activity to this patient population regularly (Table XII). In response to a statement about how confident physiotherapists felt when prescribing exercise to patients with advanced cancer, a large number of physiotherapists agreed that they were confident however a high number of physiotherapists also agreed that there is a need for further information on prescribing physical activity recommendations to patients with advanced cancer. Physiotherapists did not strongly agree that there are cues to action (e.g. such as encouragement from friends and family) that encourage patients with advanced disease to increase physical activity levels (Table XII).

Question:	Strongly Agree (n)	Mostly / Somewhat Agree (n)	Neither Agree or Disagree (n)	Somewhat / Mostly Disagree (n)	Strongly Disagree (n)
Perceived benefits and barriers:					
In my opinion being physically active is important for patients with advanced cancer	**11** (31%)	**22** (63%)	**1** (3%)	**1** (3%)	**0** (0%)
I feel that patients with advanced cancer are capable of completing physical activity programmes	**9** (26%)	**23** (66%)	**1** (3%)	**2** (6%)	**0** (0%)
I feel that patients with advanced cancer come to me for physical activity recommendations	**4** (11%)	**19** (54%)	**3** (9%)	**9** (26%)	**0** (0%)
In my opinion increasing physical activity levels in patients with advanced cancer is safe	**6** (17%)	**23** (66%)	**2** (6%)	**3** (9%)	**1** (3%)
I find providing physical activity recommendations to patients with advanced disease is usually well received	**2** (6%)	**24** (69%)	**2** (6%)	**7** (20%)	**0** (0%)
Cues to action:					
I feel that patients with advanced cancer believe they should remain physically active	**3** (9%)	**15** (43%)	**4** (11%)	**13** (38%)	**0** (0%)
I feel patients with advanced cancer will follow the advice of physical activity recommendations given	**0** (0%)	**22** (63%)	**6** (17%)	**7** (20%)	**0** (0%)
I find the families and friends of patients with advanced cancer encourage physical activity	**1** (3%)	**16** (45%)	**6** (17%)	**11** (31%)	**1** (3%)
Self-Efficacy:					
I am confident in my ability to prescribe exercise to patients with advanced cancer	**8** (23%)	**19** (54%)	**3** (9%)	**5** (14%)	**0** (0%)
I regularly prescribe physical activity recommendations to patients with advanced cancer	**10** (29%)	**20** (57%)	**3** (9%)	**2** (6%)	**0** (0%)

Table XIII Physiotherapists' views towards physical activity and advanced cancer

5.4.3. Case Study Responses

Themes and sub-themes which emerged from content analysis of therapists responses to case study scenarios are listed in Table XIII.

Theme	**Sub-theme**
Exercise Prescription	Type and Intensity of Exercise
	Need for Medical Clearance
	Complex Decision Making
	Therapists need for further CPD in this population
Benefits of Exercise	Mental Health
	Side-effects of Treatment
Physiotherapists Concerns	Increased fracture risk
	Need for thorough patient assessment
	Bone Heath of Patient
	Patient Risk of Falls

Table XIV Patient Case Studies: Themes and Sub-themes

5.4.3.1. Case Study 1: Prescribing physical activity

Physiotherapists outlined the importance of patients maintaining their physical activity levels; "*I feel physical activity is an important adjunct to this man's treatment"* (Participant (P) 17, Case Study (CS) 1). Engaging in physical activity was seen by another respondent as; "*paramount to his mental health"* (P4, CS1). When discussing exercise prescription, physiotherapists referenced the existing exercise guidelines for all cancer patients; *"I would encourage him to be active for at least 30mins 5 times per week and working to an intensity in which he is slightly puffed"* (P19, CS1). Many also stated that the patient should gauge exercise tolerance by common symptoms; *"We would discuss pacing activities within his limits of pain and energy levels"* (P7, CS1).

5.4.3.2. Case Study 1: Concerns related to physical activity

Numerous respondents reported some concern when prescribing physical activity to this patient; "*I would feel relatively comfortable although concerned with his age, mets and demands of golf*" (P04, CS1). Concern centred on the possibility of increasing harm to the patient, in many cases due to the presence of bone metastasis; *"There is a risk of bone fracture if activity is not properly prescribed"* (P23, CS1). Physiotherapists suggested adapting this patient's current activities to ensure safety and comfort for patients; *"may need to modify some of how he does his garden"* (P18, CS1), *"he may have to modify some tasks"* (P10, CS1). Only two physiotherapists suggested what these modifications may entail: one stated they would *"consider positioning, use of equipment"* (P22, CS1) and another suggested the patient could focus on *"positions to reduce strain on his back, possibly wearing a corset for some activities"* (P25, CS1). While some physiotherapists mentioned modifying activities, others suggested limiting any high intensity activities; "*Not necessarily to discourage him but to set boundaries that he should be aware of when exercising"* (P16, CS1). Responses by some physiotherapists demonstrated uncertainty about how to gauge intensity; "*I would wonder if I am working this patient at too high or low an intensity to get benefit/harm from exercise"* (P13, CS1).

5.4.3.3. Case Study 2: Prescribing physical activity

Physiotherapists were happy to initiate a discussion with this patient about physical activity; "*I would feel very comfortable discussing physical activity options"* (P26, CS2). Activities to enable functional independence and activities that were enjoyable for this patient were encouraged. Discussing physical activity was seen by 29% (11/38) of physiotherapists as an opportunity to educate this patient on the benefits of physical activity for managing cancer related symptoms and side effects of treatment. Physiotherapists recognised there may be an element of fear preventing this patient from increasing his physical activity; "*This patient may be frightened by his bone Mets"* (P20, CS2), and responses highlighted that with encouragement and reassurance the patient may increase physical activity levels; "*Hopefully with education and guidance, he may be confident to exercise"* (P23, CS2). In contrast to case study 1, respondents reported greater confidence in prescribing physical activity to the participant in case study 2.

5.4.3.4. Case Study 2: Concerns related to physical activity

In case study 2, physiotherapists indicated a need to complete a multifactorial assessment before prescribing increases in physical activity. Physiotherapists felt the patient's pre-morbid status, fatigue levels, pain levels and risk of cachexia all needed thorough assessment. The theme of causing harm to the patient arose in responses to this case study also. 18% (7/38) of physiotherapists reported a need to discuss the patient's exercise capacity with the medical team or GP prior to prescribing physical activity; "*Risk of fracture would need to be discussed at MDT level before I would discuss PA with this patient"* (P19, CS2). Concern related to physical activity prescription with this patient again centred on bone fragility; "*he is at increased risk of osteoporosis and fractures*" (P11, CS2). Pain was mentioned as an indication to limit activity by many physiotherapists; *"Stop if there is any pain or discomfort"* (P7, CS2), *"I would be guided by pain in his pelvis/hip area"* (P18, CS2). There were varying responses regarding the amount of weight bearing this patient could tolerate during physical activity; *"The type of exercise would need to consider weight bearing limitations and what alternative options there are"* (P22, CS), "*He would be suitable for non-weight bearing activities"* (P25, CS2). While many physiotherapists discussed potential aerobic activities suitable for patients, a small percentage of physiotherapists mentioned concerns in relation to prescribing resistance exercise for this patient; *"Functional strength training without specific weight resistance exercise*" (P24 CS2), "*Activity prescribed would be based on more functional activity rather than specific weight resistance exercise"* (P25 CS2).

5.5. Discussion

The majority of physiotherapists perceived physical activity to be of great benefit for patients living with advanced cancer. Despite the known benefits of remaining physically active there was some ambiguity over the optimal approach to exercise prescription to this population. The complex nature of prescribing physical activity to this patient group was a theme evident throughout qualitative responses. Physiotherapists' perceived cues to action suggest that patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels.

Physiotherapists expressed varying levels of confidence in prescribing physical activity to patients with metastatic disease. This may result in poor implementation of the positive findings of exercise trials in the clinical setting (Beaton *et al.*, 2009, Albrecht and Taylor, 2012). Despite the growing body of evidence, physiotherapists reported much

uncertainty regarding the optimal physical activity parameters for this patient group. While some exercise recommendations given by participants reflected the results of newly established research, others reflected older practices in the area of cancer exercise therapy. The high proportion of respondents working clinically for greater than ten years may have influenced their views towards physical activity. Many treatment options for patients with cancer have developed during this time, as have advances in exercise prescription (Cormie *et al.*, 2013, Okamura, 2011). As evidenced in the systemic review presented in Chapter 2, in early studies, patients with advanced cancer were excluded from many physical activity programmes due to the risks associated with bone metastasis (Adamsen *et al.*, 2009). There are now an increasing number of clinical trials in the advanced cancer population, including patients with bone metastasis (Temel *et al.*, 2009, Cheville *et al.*, 2010, Bourke *et al.*, 2011, Oldervoll *et al.*, 2011, Lowe *et al.*, 2013, Bourke *et al.*, 2014). Aerobic exercise programmes of up to twelve weeks' duration have been completed by patients with advanced cancer, with no adverse events reported (Quist *et al.*, 2012). Despite this, patients were perceived by physiotherapists as highly susceptible to injury due to their advanced stage of disease. The recommendations of clinical studies in this area should be used by physiotherapists to inform physical activity prescription to similar patient groups in clinical practice.

While physiotherapists perceived physical activity to be of benefit to patients, multiple barriers to prescribing physical activity emerged in qualitative responses. Resistance programmes were not encouraged by physiotherapists in both case studies due to concerns about pathological fractures. Despite this, recent trials prescribing resistance exercise programmes for patients with metastatic disease studies have shown very promising results. Perceived barriers are the strongest and most significant determinant of healthcare related behaviour, and it is important that the barriers reported by physiotherapists are addressed (Orji *et al.*, 2012).There is a need for more education and training around methods of adapting resistance exercise programmes for advanced cancer populations, as implemented in previous clinical studies (Temel *et al.*, 2009, Cormie *et al.*, 2013). There was also uncertainty among physiotherapist in relation to the suitability of weight bearing activity to this patient group. No differences in the rate of pathological fracture have been reported in previous studies comparing weight bearing to non-weight bearing activity (Bunting and Shea, 2001) and pain free weight bearing activity should be encouraged (Riccio *et al.*, 2007). There is growing evidence supporting the efficacy of appropriately designed and supervised resistance and weight bearing activities to patients with advanced cancer. Increased awareness of this research may help to decrease physiotherapists' perceived barriers to prescribing physical activity.

Educational efforts targeting physiotherapists' concerns and misconceptions about the prescription of physical activity for patients with advanced disease may help to reduce the level of concern related to prescribing physical activity in this population. In-service training and journal clubs on the topic of physical activity and advanced disease could be used to increase physiotherapist's exposure to the evolving medical literature in this area.

Physiotherapists' perceived cues to action suggest patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels. Given the importance of physical activity in cancer control, physiotherapists have an increasingly important role in introducing patients to an exercise environment, but also in educating both patients and their carers on the important role of physical activity in maintaining and optimising physical function (Courneya and Friedenreich, 2007). Responses in this study indicate that further efforts are needed to educate patients living with advanced cancer on the role of exercise in managing symptoms and improving function. Additionally, physiotherapists' perceptions of patients' families and friends' supportiveness for physical activity suggest that education efforts should also extend to this group. Consultation with a physiotherapist may serve as an important cue to action for patients with advanced disease to maintain or increase physical activity levels, as advice on the benefits of exercise can be shared and discussed. Additional cues to action are also needed. One study examining the attitudes of Canadian oncologists towards recommending exercise to patients with cancer found a relatively low proportion of oncologists (29.5%) felt that their patients were capable of exercising during treatment (Jones *et al.*, 2005), suggesting that healthcare professionals may benefit from education and training in the area of exercise oncology. All healthcare professionals can act as external triggers to encourage patients to increase physical activity levels during or after cancer treatment. Physiotherapists should advocate for the role of physical activity in advanced disease and encourage clinicians to promote physical activity in this population (Daley *et al.*, 2008).

5.6. Study Limitations

A detailed medical history was not provided for the case studies provided in this study. The provision of more detail relating to case studies may have influenced physiotherapist responses regarding physical activity prescription. The case studies were generated specifically for use in this research and its validity requires additional testing as no pilot

study was conducted on the material. However, case studies were developed based on patient cases observed in a national cancer centre and therefore have good clinical applicability and relevance.

5.7. Study 5a: Conclusion

The majority of physiotherapists perceived exercise to be of great benefit for patients living with advanced cancer, and regularly prescribe physical activity to this patient group. Despite this, physiotherapists reported ambiguity over the optimal parameters for physical activity prescription. More work is needed to disseminate the results of research in this area among physiotherapists. Physiotherapists' perceived cues to action suggest patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels. Physiotherapists should advocate for the benefits of physical activity for patients with advanced disease.

Chapter 5b: Physical Activity and Advanced Cancer: The Views of Oncology and Palliative Care Physicians in Ireland

5.8. Chapter 5b: Introduction

This chapter will examine the beliefs of Irish physicians regarding physical activity recommendations for patients with advanced cancer and explore any potential concerns regarding physical activity engagement in this population using a scenario-based survey. The work has been peer reviewed and published in the *Irish Journal of Medical Science* (Gráinne Sheill, Emer Guinan, Linda O'Neill, David Hevey & Juliette Hussey (2017): Physical Activity and Advanced Cancer: The views of Oncology and Palliative Care Physicians in Ireland DOI: 10.1007/s11845-017-1677-x) (Appendix 6).

Patients receiving or completing treatment for advanced cancer have substantially lower physical activity levels than the general population. In one study that examined the

physical activity levels of 71 patients with metastatic breast cancer, participants attained only half of the steps per day achieved by age-matched healthy controls (5,434 ± 3,174 vs. 9,635 ± 3,327) (Yee *et al.*, 2014). Additionally, 85% of participants did not achieve >8,000 steps a day: the level at which most health benefits are achieved in older populations (Ewald *et al.*, 2014). Systematic reviews provide evidence that higher physical activity levels in patients with advanced cancer are associated with greater quality of life and improved physical status (Beaton *et al.*, 2009, Albrecht and Taylor, 2012). Therefore, there is a need to explore ways to maximise physical activity levels in patients at this stage of the cancer trajectory.

As outlined in Chapter 5a, all healthcare professionals can act as external triggers to encourage patients to increase physical activity levels during or after cancer treatment. In particular, evidence suggests that oncologists may play an important role in enhancing exercise levels in patients with cancer (Jones *et al.*, 2005). The majority of patients with cancer prefer oncologist initiated exercise discussions to discussions they initiate themselves (Jones and Courneya, 2002). However, a UK study found 56% of breast care oncologists and surgeons did not routinely discuss physical activity with their patients (Daley *et al.*, 2008). Similarly, in a US study 38% of oncologists and surgeons reported that they did not enquire about patients' activity levels (Karvinen *et al.*, 2010). Collaboration with physicians around physical activity goals has been shown to improve patients' healthcare outcomes (Martin *et al.*, 2005). A single-blind randomised control trial demonstrated that a brief oncologist prompt to exercise during treatment consultations significantly increased physical activity in patients with newly diagnosed breast cancer by a mean of 3.4 MET-hour per week (95% CI 0.7-6.1 MET-h per week) (Jones *et al.*, 2004).

Oncologists may also be an important source of motivation for patients living with advanced cancer. Studies examining the attitudes of oncology care providers towards recommending exercise for patients with early stage cancer have identified limited knowledge on how or where to refer a patient to exercise and safety concerns as the main barriers to discussion about exercise (Park *et al.*, 2015, Nadler *et al.*, 2017). However, there is little information regarding clinicians' attitudes towards recommending physical activity to patients with advanced stages of disease. Given the many physical and psychological side effects of advanced cancer, oncologists' attitudes towards this group may differ from the attitudes towards prescribing physical activity to patients with early stage disease. Additionally, the presence of bone metastases in many patients with

advanced cancer may affect the perceptions of oncologists around the safety of exercise in this population.

5.9. Study aims and objectives

The overall aim of this study was to examine the views of Oncology and Palliative Care Physicians in Ireland towards physical activity in patients with advanced cancer. The specific objectives of this study were:

- To determine the beliefs of Irish physicians regarding physical activity recommendations for patients with advanced cancer
- To explore any potential concerns regarding physical activity engagement in this population using a scenario based survey.

5.10. Materials and Methods

5.10.1. Study design

This study used a mixed-methods study design, involving both quantitative and qualitative questions as described in Chapter 2 (Section 2.1.1 & Section 2.2.1). Data was collected using an online questionnaire. Participants received the survey by email, via their contact details listed in the Irish medical directory or palliative care group. A reminder email was sent at 4 weeks.

5.10.2. Sampling and Recruitment

The study was conducted among a convenience sample of consultant radiation and medical oncologists in Ireland, and members of the Irish palliative care consultants group. Physicians were senior doctors who had completed speciality training in the area of oncology or palliative care.

5.10.3. Study Instrument

An anonymous online survey (via SurveyMonkey.com, LLC, San Mateo, CA, USA) was created. Participants received the survey by e-mail, via contact details listed in the Irish

medical directory or palliative care group. Consent was implied through completion of the survey. All response data was stored on a password accessed server. A reminder e-mail was sent at 4 weeks by the study gatekeeper.

The survey included demographic questions, ten attitude questions (rated on a 7-point Likert scale, ranging from 'strongly agree' to 'strongly disagree'), and questions relating to two case studies about patients with bone metastases. These two contrasting case studies were chosen as they were representative of typical presentations of patients with bone metastases attending an outpatient oncology clinic in a national cancer centre.

Case Study 1:
Patient 1 is 86 years old with widespread axial metastases secondary to prostate cancer. He has few co-morbidities and has been active all his life. During his consultation he mentions that he plans on remaining active and continuing activities, which include manual labour in the garden and playing golf every day.

Case Study 2:
Patient 2 has stage IV prostate cancer with bone metastases to his proximal femur and pelvis. He has a poor relationship with physical activity and multiple co-morbidities. He feels that his diagnosis with cancer is a reason to limit his physical activity.

Physicians were asked to provide open text comments describing whether they would be happy to provide physical activity recommendations for the patients and to outline concerns, if any, relating to physical activity prescription in the cases provided. An open ended text box was provided at the end of the survey for additional comments regarding exercise prescription for patients with advanced cancer.

5.10.4. Ethical Approval

The study protocol was approved by the Trinity College Dublin Faculty of Health Sciences Ethics Committee (Ref: 20150609).

5.10.5. Data analysis

Descriptive data are presented as the mean (standard deviation (SD)) for continuous data and frequency (percentage) for categorical data. Text-based responses to open-

ended questions related to the case studies were analysed using content analysis (Hsieh and Shannon, 2005). Each response was coded independently by two of the authors, and codes were compared for inter-rater agreement.

5.11. Results

5.11.1. Participant Characteristics

A total of 98 radiation oncologists, medical oncologists and palliative care physicians were contacted, and 40 responses were received, a response rate of 41%. Details of the demographic profile of participants are presented in Table XIV. The majority of respondents were specialised in palliative care (57%, n=23) and were practicing for over 10 years (82%, n=32). The majority of physicians (55%) reported discussing physical activity with over half of their patient caseload.

Variable	N	%
Speciality		
Radiation Oncology	9	23%
Medical Oncology	8	20%
Palliative Care	23	57%
Number of Years Practicing		
1-5 years	1	3%
5-10 years	7	17%
10-20 years	19	48%
Over 20 years	13	32%
Primary Tumour Group		
Breast	5	22%
Genitourinary	6	26%
Multiple	12	52%
Primary tumour group not identified	17	42%
Number of physicians initiating discussions about PA during consultations		
With 0-25% of patients	2	5%
With 25-50% of patients	14	35%
With 50-75% of patients	10	25%
With 75-100% of patients	12	30%
No response given	2	5%

Table XV Demographic Characteristics of Physicians

PA: Physical Activity

Table XV provides a summary of physicians' responses to the structured questionnaire. All physicians agreed with statements 1 and 2, that physical activity is important and safe for patients with advanced cancer. The majority of physicians (67% n=26) agreed patients look to them for physical activity recommendations and 74% (n=23) felt that patients would follow any physical activity recommendations given. Less than half of physicians (44%, n=17) agreed that the family and friends of patients encourage physical activity. A large proportion of physicians (77%, n=30) expressed a need for more information on providing physical activity recommendations to this patient cohort.

	Strongly Agree	Mostly Agree	Somewhat Agree	Neither Agree or Disagree	Somewhat Disagree	Mostly Disagree	Strongly Disagree
In my opinion being physically active is important for patients with advanced cancer	**22 (**56 %)	**14 (**36 %)	**2 (**5 %)	**0 (**0 %)	**1 (**3%)	**0 (**0 %)	**0 (**0 %)
In my opinion being physically active is safe for patients with advanced cancer	**8 (**21 %)	**26 (**67 %)	**5 (**13 %)	**0 (**0 %)	**0 (**0 %)	**0 (**0 %)	**0 (**0 %)
My fellow clinicians feel physical activity is important for patients with advanced cancer.	**5 (**13 %)	**16 (**41 %)	**9 (**23 %)	**7 (**18 %)	**0 (**0 %)	**1 (**3 %)	**1 (**3 %)
I feel that patients with advanced cancer believe they should remain physically active	**2 (**5 %)	**8 (**21 %)	**17 (**44 %)	**1 (**3%)	**10 (**26%)	**1 (**3%)	**0 (**0 %)
I feel that patients with advanced cancer look to me for physical activity recommendations	**1 (**3%)	**12 (**31%)	**13** (33%)	**8 (**21 %)	**3 (**8 %)	**2 (**5 %)	**0 (**0 %)
I find that providing physical activity recommendations to patients with advanced disease is usually well received	**4 (**10 %)	**16 (**41 %)	**12 (**31 %)	**4 (**10 %)	**3 (**8 %)	**0 (**0 %)	**0 (**0 %)
I feel that patients with advanced cancer will follow the physical activity recommendations given	**2 (**5 %)	**7 (**18 %)	**20 (**51 %)	**4 (**10 %)	**5 (**13 %)	**1 (**3 %)	**0 (**0 %)
I find that families and friends of patients with advanced cancer encourage physical activity	**1 (**3%)	**6 (**15%)	**10 (**26%)	**7 (**18 %)	**8 (**21 %)	**7 (**18 %)	**0 (**0 %)
I am confident in my ability to prescribe exercise to patients with advanced cancer	**1 (**3%)	**9 (**23 %)	**10 (**26%)	**9 (**23 %)	**3 (**8 %)	**5 (**13 %)	**2 (**5 %)
I feel that I need more information on providing physical activity recommendations to patients with advanced cancer	**7 (**18 %)	**16 (**41 %)	**7 (**18 %)	**6 (**15%)	**1 (**3%)	**2 (**5 %)	**0 (**0 %)
I regularly consider onward referral to physiotherapy for this patient group	**13** (33%)	**7 (**18 %)	**9 (**23 %)	**4 (**10 %)	**0 (**0 %)	**4 (**10 %)	**2 (**5 %)

Table XVI Physicians Attitudes towards Physical Activity

5.11.2. Case study responses

There were a number of common concerns with exercise prescription reported by physicians in relation to the two case studies presented (Table XVI). Further information on responses is described below. Common concerns reported by physicians were also mentioned in the context of associated risk factors. For example, while physician were concerned about the risk of spinal cord compression in metastatic patients, this was related to the risk of vertebral fracture and spinal instability. Importantly, a number of physicians associated increased physical activity levels with the aggravation of symptom control e.g. pain control and fatigue levels.

Concerns reported by physicians (n, %)	**Associated risk factor(s) identified by physicians**
Pathological Fracture (26, 65%)	Presence of bone metastases Osteoporosis Androgen Deprivation Therapy Sedentary Behaviour
Spinal Cord Compression (14, 35%)	Vertebral Fracture Spinal Instability
Aggravation of symptom control (8, 20%) Eg. Fatigue, Pain	Sudden increase in physical activity levels
Musculoskeletal Injury (5, 12%)	Poor manual handling techniques Concern re. heavy lifting Poor baseline activity levels

Table XVII Physical Activity Concerns Reported by Physicians.

The associated risk factors are also provided. For example, physicians were concerned about pathological fractures due to the presence of bone metastases.

Case Study 1

All physicians were happy to discuss physical activity with this patient. They emphasised the need for this patient to continue to maintain daily activity levels. "*I would routinely encourage patients to maintain existing levels of physical activity if they feel they are able*" *(PHY09).* Physicians described the many benefits associated with prescribing physical activity including limiting the side effects of treatments, reducing cardiovascular risk, weight management, limiting cachexia/muscle loss and fatigue. There was disagreement among physicians about the suitability of weight bearing exercise for this patient *"On ADT there is a risk of muscle loss and osteopenia so weight bearing exercise*

is important" (PHY011), "(he) would need not to engage in weight bearing activities" (PHY027). 5% of physicians considered onward referral to spinal surgeons and physiotherapy for further assessment.

Case Study 2

All physicians, except one, stated they would be happy to recommend physical activity to this patient. The participant who reported that they would not discuss physical activity with this patient stated that they would like to know this patient's Mirel's fracture risk score, *"….might need expert ortho/physio advice re weight bearing if fracture risk high"* (PHY10). The majority of physicians mentioned the need for a multifactorial assessment of this patient prior to physical activity recommendation. *"Current performance status and pain control plus review/knowledge of imaging would inform any recommendations (PHY012)".* Physicians commented on this patient's poor baseline activity levels, *"I think this gentleman will struggle to exercise…he's definitely someone that I would consider referral for an exercise programme as it would be customised to him and hopefully he may adhere to it"* (PHY011). Physicians considered onward referral to orthopaedic teams and outpatient physiotherapy for advice regarding weight bearing exercise and fracture risk.

In the additional comments for this survey, physicians commented on the lack of exercise prescription services available for patients living with advanced cancer *"There is no mechanism to prescribe exercise in a supervised setting"* (PHY07). A small number of participants mentioned a poor attitude towards prescribing exercise in Ireland *"Should be encouraged, it's free and in my experience oncologists prefer to prescribe a drug, despite good quality evidence"* (PHY020). *"Cult of mind yourself, do nothing and take supplements as opposed to high protein diet and exercise is strong in Ireland"* (PHY027).

5.12. Discussion

The results of this study demonstrate that medical and radiation oncologists, and palliative care physicians consider physical activity to be important for patients with advanced cancer. Additionally, all respondents believed that physical activity is safe for patients with advanced cancer. The majority of physicians reported that patients look to them for physical activity recommendations and many physicians identified a need for more information on providing physical activity recommendations for patients with advanced cancer. The percentage of physicians that reported discussing physical activity with their caseload appears similar to the number of oncology physicians

discussing physical activity with patients in comparable studies from Canada, Australia and the UK (Jones *et al.*, 2005, Daley *et al.*, 2008, Keogh *et al.*, 2015). Cancer patients who report that their oncologist discussed exercise during treatment consultations have been shown to have higher levels of exercise during subsequent treatment (Jones and Courneya, 2002), highlighting the benefit of discussion between physicians and patients regarding physical activity. A large proportion of physicians in this study were confident that patients would comply with any exercise recommendations given but were not confident in their own ability to prescribe exercise, highlighting the need for greater education around the role of exercise for patients with advanced cancer for health care providers. Interestingly, physiotherapists in Chapter 5a looked to physicians regarding instructions for exercise prescription in this cohort, however physicians themselves would look to physiotherapists for advice. This highlights the need for further education regarding physical activity in advanced disease among all healthcare professionals. There is a growing body of evidence detailing the benefits of aerobic and resistance exercise for patients with symptoms of advanced stage disease, including fatigue and breathlessness (Bourke *et al.*, 2011, Bourke *et al.*, 2014) as well as bone or visceral metastases (Oldervoll *et al.*, 2006, Cormie *et al.*, 2013). There is a need to create educational opportunities across oncology related specialities to disseminate these updates in exercise oncology literature. Greater knowledge on the many benefits of exercise in this population may encourage more physicians to initiate discussions about physical activity with patients.

Physicians expressed many concerns regarding physical activity in case studies involving patients with bone metastases, centred on the risk of pathological fracture and the risk of spinal cord compression. This is a significant issue for patients with bone metastases. However, as outlined in Chapter 1, there is evidence that individually prescribed physical activity programmes can be safely introduced for patients with many symptoms of advanced disease, including bone metastases (Oldervoll *et al.*, 2006, Bourke *et al.*, 2011, Oldervoll *et al.*, 2011, Cormie *et al.*, 2013, Bourke *et al.*, 2014). In these studies, which describe no adverse events, all physical activity programmes were prescribed to reduce the loading and sheer forces put on an area of metastases. Exercise prescription by exercise specialists may be essential for safe and appropriate exercise participation in this cohort. If a risk of fracture is perceived as a barrier to exercise, tools to stratify risk of fracture can be used. Mirels' classification system for impending pathologic fracture is a valid screening tool for metastatic lesions in long bones (Jawad and Scully, 2010). As discussed in Chapter 1, the Mirels' system classifies the risk of pathologic fracture based on scoring four variables on a scale of 1-3: location

of lesion, radiographic appearance, size, and pain. An overall score is calculated, and a recommendation for or against prophylactic fixation is made (Jawad and Scully, 2010). While traditionally used to identify patients in need of prophylactic fixation, this classification system could also be used to help health professionals identify patients at low risk of pathological fracture and suitable for exercise interventions.

Many physicians in this survey considered onward referral to further exercise prescription services such as supervised exercise programmes or outpatient physiotherapy; however, others commented on the lack of these services nationally. Referral to exercise specialists is not a part of the standard care received by oncology patients in Ireland. Irish cancer survivors have identified a striking lack of contact with health professionals that might be influential in facilitating recovery and rehabilitation (Ivers, 2009). In contrast, the American College of Surgeons Commission on Cancer produced a standard that all accredited institutions provide cancer rehabilitation services, which has spurred healthcare providers in the United States to develop cancer rehabilitation programmes across diverse delivery settings (Surgeons, 2016). Additionally, the Institute of Medicine recommends the use of survivorship care plans that include recommendations and information regarding health promoting behaviours (Salz *et al.*, 2012). Despite this, the integration of rehabilitation and survivorship exercise into standard clinical cancer care, continues to remain the exception rather than the norm (Santa Mina *et al.*, 2012). Established clinical rehabilitation models such as cardiac rehabilitation and pulmonary rehabilitation incorporate supervised, progressive exercise training with multi-disciplinary management of disease specific side-effects. These clinical models may be easily transferrable to the cancer context and provide a way to incorporate rehabilitation into the cancer care model in Ireland.

When compared to Chapter 5a, there are many similarities in the views of both clinicians and physiotherapists towards patients with metastatic bone disease. Both groups feel physical activity is safe and important to this patient cohort however both individual groups demonstrated a need for further information in the area of physical activity and advanced disease. Physiotherapists require further information re. exercise prescription in advanced cancer, and clinicians would like additional referral options for patients with advanced cancer to access tailored exercise prescription.

5.13. Study 5b: Conclusion

Overall, oncologists and palliative care physicians perceived exercise to be of benefit for patients with advanced cancer. Concerns over exercise prescription to patients with bone metastases highlight the need to disseminate the evidence on the benefits of physical activity for patients with advanced cancer to all healthcare professionals. This may encourage greater discussion between physicians and patients around physical activity during consultations.

6. Chapter 6: The ExPeCT Randomised Controlled Trial

6.1. Introduction

This chapter describes the ExPeCT (Exercise Prostate Cancer and Circulating Tumour Cells) randomised controlled trial. The primary aim of the ExPeCT trial was to examine if the evasion of immune editing by circulating tumour cells (CTCs) is an exercise-modifiable mechanism in obese men with prostate cancer. Biological outcomes associated with this aim are not examined as part of this thesis; however, the following chapter presents the results of a number of secondary outcomes of the ExPeCT trial. I co-ordinated the ExPeCT trial, liaising with site leads and Cancer Trials Ireland, trial sponsor, on activities from trial initiation to trial close-out. My responsibilities also included co-ordinating the activities of the six sites involved in the ExPeCT trial. I was responsible for trial implementation, particularly exercise screening, prescription and supervision, and participant management including recruitment, consenting and follow up and data management. I was first author on the publication of the protocol for the ExPeCT Trial (Sheill, G., Brady, L., Guinan, E., Hayes, B., Casey, O., Greene, J., Vlajnic, T., Cahill, F., Van Hemelrijck, M., Peat, N. and Rudman, S., 2017. The ExPeCT (Examining Exercise, Prostate Cancer and Circulating Tumour Cells) trial: study protocol for a randomised controlled trial. *Trials*, *18*(1), p.456. (Appendix 7)).

In many instances, the goal of therapy in advanced prostate cancer is one of palliation as opposed to cure. As such, it is necessary to assess the impact of interventions which may improve quality of life. Quality of life measurement in prostate cancer therapy has become an essential component of clinical trial evaluation (Ganz, 2011). Additionally, advanced cancer patients are encouraged to remain physically active. International exercise oncology guidelines suggest that cancer patients, including those with bone metastases, should avoid inactivity (Schmitz *et al.*, 2010). Physical activity levels of 9 MET-h/wk has been previously shown to be associated with a 33% reduction in all-cause mortality following early stage prostate cancer (Kenfield *et al.*, 2011). Therefore, there is a need to investigate how patients with metastatic disease tolerate physical activity programmes. The ExPeCT trial aimed to examine the effect of a six-month aerobic exercise intervention on quality of life outcomes in men diagnosed with metastatic prostate cancer. The ExPeCT study also aimed to assess the safety and feasibility of introducing a structured aerobic exercise intervention to an advanced prostate cancer population. The hypotheses of this chapter are:

- A six month exercise intervention will result in improvements in the quality of life of men with advanced prostate cancer.
- A six month exercise intervention will result in improvements in sleep, pain, depression, stress, physical function and physical activity levels in men with advanced prostate cancer.
- Men with advanced prostate cancer can safely adhere to a six month aerobic exercise intervention.

6.2. Methods

6.2.1. Study Population

This international multi-centre prospective study recruited men living with metastatic prostate cancer through hospital outpatient clinics between October 2014 and March 2017. Men deemed eligible after initial screening were randomly assigned to either a six month exercise program or to a control arm.

Eligibility criteria included

1. Written informed consent obtained before any study-related procedures
2. Aged ≥ 18 years and male
3. Histologically confirmed diagnosis of prostate adenocarcinoma
4. M1 metastatic disease as confirmed by computed tomography (CT)/magnetic resonance imaging (MRI) or by bone scan, excluding patients who only have nodal metastatic disease
5. Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to randomisation
6. Capable of participating safely in the proposed exercise as assessed and signed off by a treating physician involved in ExPeCT recruitment.

Exclusion criteria included

1. Patients with a history of radical prostatectomy
2. Patients with other known malignancy (except non-melanoma skin cancers or fully excised carcinoma in situ at any site).

6.2.2. Participant Enrolment Procedure

The ExPeCT Trial opened in two Irish centres in October 2014. Due to slow recruitment rates at both sites over the initial four months, the decision was made to expand the ExPeCT trial to a further three Irish Hospitals. Additionally, the decision was made to seek sponsorship for the ExPeCT trial from Cancer Trials Ireland, to provide the ExPeCT team with assistance when completing multiple applications for ethical approval, and to enable Cancer Trials Ireland nurses working in hospital clinics to recruit patients to ExPeCT.

Recruiting sites included Guy's and St Thomas's Hospital, London (Inducted May 2015), the Mater Misericordia Hospital Dublin (Inducted March 2016), Beaumont Hospital, Dublin (Inducted April 2016), St. James's Hospital, Dublin (Inducted November 2014), Tallaght Hospital, Dublin (Inducted March 2015) and St Luke's Radiation Oncology Network, Dublin (Inducted May 2016). The ExPeCT Trial received sponsorship from Cancer Trials Ireland in five Irish Hospitals (Figure 20). As outlined in Chapter 2, section 2.4, ExPecT received ethical approval from all sites (Appendix 2).

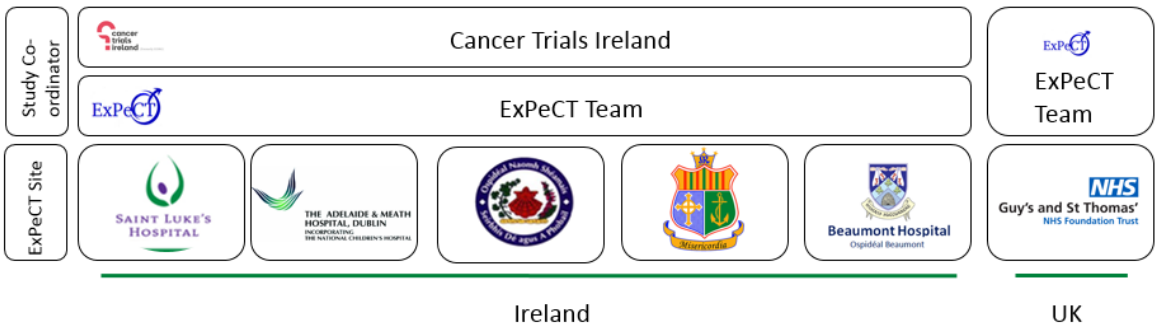


Figure 20 Overview of ExPeCT Trial Sites

Potential patients were enrolled to the study on the basis of the inclusion/exclusion criteria detailed. Any queries about eligibility were addressed directly to the Chief Investigator. I liaised with key personnel involved in the ExPeCT Trial (Figure 21) to co-ordinate the enrolment of patients with members of the research team based in medical oncology clinics at each recruiting site. All tasks were delegated by the principle investigator at each site. Study training records were kept for each member of the research team (Appendix 8).

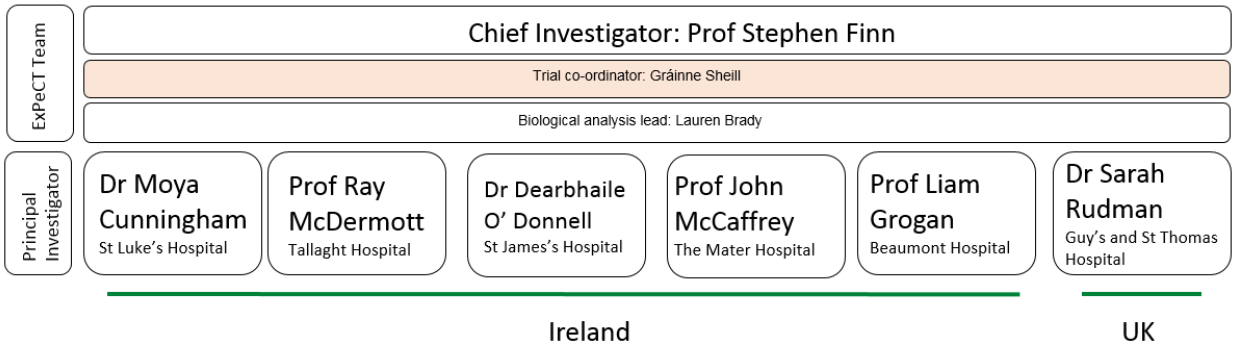


Figure 21 Key ExPeCT Personnel

A flowchart outlining the ExPeCT trial is included here (Figure 22). All participants received a Participant Information Leaflet on the ExPeCT Trial (Appendix 9). Informed consent (Appendix 10) was obtained by clinic staff or a member of the ExPeCT research team according to the requirements of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP). Upon registration of new participants, a signature confirming eligibility for the trial was obtained from a treating physician involved in ExPeCT recruitment. Each registered patient received a unique participant identifier number (PIN). In order to ensure random allocation of participants to each study group, the computer programme Graphpad was used to randomly assign a treatment group to each PIN. When issuing each PIN, two gatekeepers (1 in Ireland and 1 in the UK) informed the research team of the treatment allocation of the participant. If a participant chose to withdraw from the study, all data obtained up to the point of withdrawal was carried forward unless requested otherwise.

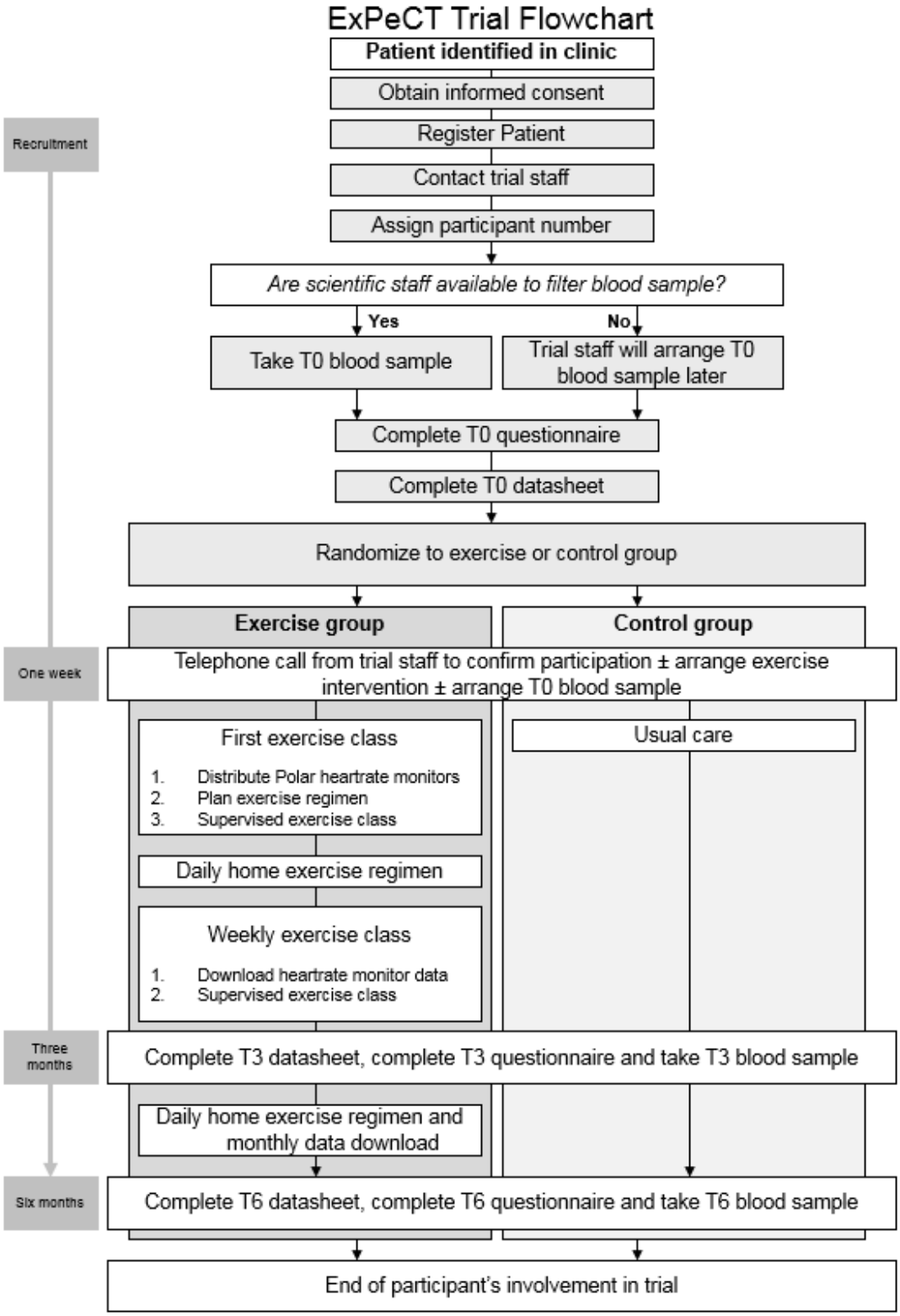


Figure 22 ExPeCT Trial Flowsheet

6.2.3. Measures

The measures used in the ExPeCT study are described in detail in Chapter 2. Section 2.1.1 describes the psychometric properties of each measure. In brief, socio-demographic and treatment details were collected for all patients (Appendix 11). All participants also completed a detailed subjective questionnaire (Appendix 12) after recruitment at baseline, and again at T3 (3 months) and T6 (6 months). The ExPeCT Questionnaire included the following outcomes:

1. Background details (age at diagnosis, domiciliary situation, comorbidities, recent medications)
2. Smoking and alcohol
3. Sleep (Pittsburgh Sleep Quality Index)
4. Stress (Perceived Stress Scale – 4)
5. Depression (PHQ-9)
6. Quality of Life (FACT-P)
7. Memory and cognition
8. Physical activity

6.2.4. Intervention

6.2.4.1. Exercise Programme

The exercise group participated in a 6-month moderate to vigorous intensity aerobic exercise programme comprising a weekly class and a home-based aerobic exercise programme. From baseline to T3, participants in the exercise arm met in small groups with a chartered physiotherapist for 1 hr per week. Participants recruited in St. Luke's, the Mater, Beaumont and the Beacon Hospital completed exercise classes in the Clinical Research Facility in St. James's Hospital or in the Physiotherapy Gym at Tallaght Hospital. Participants recruited in St. James's Hospital completed exercise classes in the Clinical Research Facility at St. James's Hospital, and those recruited at Tallaght Hospital and Guy's Hospital completed exercise classes in the physiotherapy departments at their local sites. I prescribed and delivered the exercise intervention to all patients recruited at Irish sites.

During the first class the participants received an introduction to the format of the exercise programme and were educated on safe exercise practices and strategies to monitor exercise exertion. Each exercise participant received, and was educated about using, a Polar heart rate monitor for the duration of the study. Documentation was completed by the physiotherapist at each class session (Appendix 13).

Participants exercised to a prescribed heart rate range during class and home sessions. HR was progressed in intensity and duration during months 1 and 2 of the programme to reach the target 3hr per week (180min/week) of moderate-to-vigorous intensity activity from month 3 onwards (Table XVII). Participants were encouraged to achieve this target exercise in six 30min sessions throughout the week. However, flexibility was allowed to facilitate longer or shorter session to a total of 180 min/week. Each exercise session was required to be of at least 10min duration in line with standard exercise guidelines (Wasserman and McIlroy, 1964).

During months 1–3, data from the Polar heart rate monitor was downloaded weekly to monitor exercise adherence. Participants were scheduled to attend the research centre once monthly from T3 to T6 to download data and encourage ongoing adherence to the programme. In addition, participants received weekly telephone contact from the ExPeCT research team from T3 to T6 to encourage adherence.

The control group were not given specific advice regarding exercise beyond that considered usual medical care, and were not invited to participate in the aerobic exercise group. Participants were reviewed at T3 and T6 following the baseline visit and anthropometric measurements and further blood samples taken. Participants assigned to the control group were offered a personal exercise advice session following completion of the T6 assessment.

Supervised Exercise Classes		**Exercise Intensity (%HRR) Baseline Fitness Groups**			**Duration**
		Poor	**Fair**	**Average**	**Minutes**
Month 1	Week 1	40-50%	50-60%	55-65%	20
	Week 2	40-50%	50-60%	55-65%	20
	Week 3	45-55%	55-65%	60-70%	20
	Week 4	45-55%	55-65%	60-70%	30
Month 2	Week 5	50-60%	60-70%	65-75%	30

	Week 6	50-60%	60-70%	65-75%	30
	Week 7	55-65%	65-75%	65-75%	30
	Week 8	55-65%	65-75%	65-75%	30
Month 3	Week 9	60-70%	65-75%	65-75%	30
	Week 10	60-70%	65-75%	65-75%	30
	Week 11	60-75%	65-75%	65-75%	30
	Week 12	60-75%	65-75%	65-75%	30

Table XVIII Exercise Intensity during supervised classes

6.2.4.2. Exercise prescription

Participants were asked to self-rate their baseline activity levels as one of three categories as per American College of Sports Medicine (ACSM) guidelines: 1) Sedentary or minimally active, not completing any moderate to vigorous activity (equivalent to poor fitness levels) 2) Sporadic physical activity, suboptimal exercise (equivalent to fair fitness levels) 3) Habitual physical activity, regular moderate to vigorous exercise (equivalent to average fitness levels).

Exercise intensity was prescribed using individualised heart rate reserve (HRR) ranges in accordance with the ACSM guidelines. Heart rates were monitored objectively using Polar heart rate monitors. Polar heart rate monitors have proven to be an acceptable means of monitoring activity intensity (Broderick *et al.*, 2013). The following formula was used to calculate HRR and heart rate (HR) range prescriptions: (target % × [maximum HR – resting HR] + resting HR). For each participant, age-predicted maximal HR was calculated using the following equation: (206.9 – [0.67 × age]) (Kohl *et al.*, 1990). Participants with self-rated 'poor' fitness levels (category 1) commenced the programme at an aerobic intensity of 40–50% HRR. Those with self-rated 'fair' fitness levels (category 2) commenced the programme at an aerobic intensity of 50–60% HRR, and those with self-rated 'average' fitness levels (category 3) commenced the programme at 55–65% HRR. The duration and frequency of the home exercise programme sessions is outlined in Table XVIII.

Patients were also encouraged to use the Borg Breathlessness Scale to self-monitor exercise intensity. Using this scale, participants provided a subjective rating of perceived exertion. It is a widely used and reliable indicator to monitor and guide exercise intensity (Wilson and Jones, 1991). The scale allows individuals to subjectively rate their level of exertion during exercise and can be used to correlate exertion levels with exercise heart

rates (Borg, 1982). In particular, the Borg scale was used with participants on beta blockers as measures of exercise intensity are inaccurate or dampened on these medications and Polar monitors may not reflect an accurate heart rate during exercise (Levinger *et al.*, 2004).

Exercise modality used for exercising during the supervised class was prescribed with according to an established clinical algorithm which aimed to avoid loading metastatic bones or avoiding high risk movements (Cormie *et al.*, 2013).

Home based walking programme		**Exercise Intensity (%HRR) Baseline Fitness Groups**			**Time**	
		Poor	**Fair**	**Average**	**Days/week**	**Duration (minutes)**
Month 1	Week 1	40-50%	50-60%	55-65%	2	20
	Week 2	40-50%	50-60%	55-65%	3	20
	Week 3	45-55%	55-65%	60-70%	3	20
	Week 4	45-55%	55-65%	60-70%	3	30
Month 2	Week 5	50-60%	60-70%	65-75%	3	30
	Week 6	50-60%	60-70%	65-75%	4	30
	Week 7	55-65%	65-75%	65-75%	4	30
	Week 8	55-65%	65-75%	65-75%	5	30
Month 3	Week 9	60-70%	65-75%	65-75%	5	30
	Week 10	60-70%	65-75%	65-75%	5	30
	Week 11	60-75%	65-75%	65-75%	5	30
	Week 12	60-75%	65-75%	65-75%	5	30
Month 4	Weeks 13-16	60-75%	65-75%	65-75%	6	30
Month 5	Weeks 17-20	60-75%	65-75%	65-75%	6	30
Month 6	Weeks 12-24	60-75%	65-75%	65-75%	6	30

Table XIX Home based exercise intensity

6.2.5. Patient withdrawal and off study procedure

Patients were free to withdraw from participation in ExPeCT at any time upon request. An off study form (Appendix 14) was completed and sent to the ExPeCT Research Team for all patients who withdrew from the study or left due to another reason (e.g study completion, extraordinary medical circumstances, lost to follow up etc).

6.2.6. Incident Reporting

The occurrence and severity of any incidents, from the time of consent to completion of the programme at six months, was recorded by the trial co-ordinator on a standardised reporting form (Appendix 15).

6.2.7. Statistical Analysis

All statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) (Version 20) for Windows (IBM, Somers, NY, USA). An intention-to-treat (ITT) approach was used. Descriptive statistics were used to profile the demographic data and disease characteristics as well as quality of life, depression, sleep, stress and memory symptom severity. The baseline values for the demographic data, disease characteristics and outcome measures between the exercise and control groups were compared using either a t-test or a χ^2 -test.

A general linear model was used to evaluate the mean and standard deviation (s.d.) values, and the differences between the group outcomes (quality of life, depression, sleep, stress and memory) at the baseline, T3 and T6, and to model the outcomes as a function of the main group effect (group differences) and main time effect. As such, statistical results are presented both in terms of between group differences at baseline, T3 and T6 and also in terms of change over time, with the control group used as the reference group. Both stability and repeated relationship analyses were conducted using generalised estimation equations (GEE). An interaction term (group x time) was added to each model to investigate the effect of exercise and time. The changes in study outcome values (quality of life, depression, sleep, stress and memory) from baseline to follow-up periods (third and sixth months) were expressed in both the walking-exercise and control groups. The general linear model was used to model the outcomes as a function of the main effect (group differences). All the tests involved a two sided significance level of $a = 0.05$.

6.3.Results

6.3.1. Patient Characteristics

Between October 2014 and March 2017 157 patients were screened for participation in ExPeCT, of which 67 were consented and randomised to the trial, representing a recruitment rate of 43% (Figure 23). A further breakdown of patients recruited to each site is shown in Table XIX. A total of 32 participants were randomly assigned to exercise control and 35 participants were randomly assigned to the control group. A total of 52 (78%) of the participants completed the six-month assessment. The proportion of patients lost to follow-up was higher in the exercise group (24%) than in the control group (14%) (p=.048). Reasons for loss to follow-up included withdrawal (n=3), symptoms associated with progressing disease (n=8), and reasons unknown (n=4).

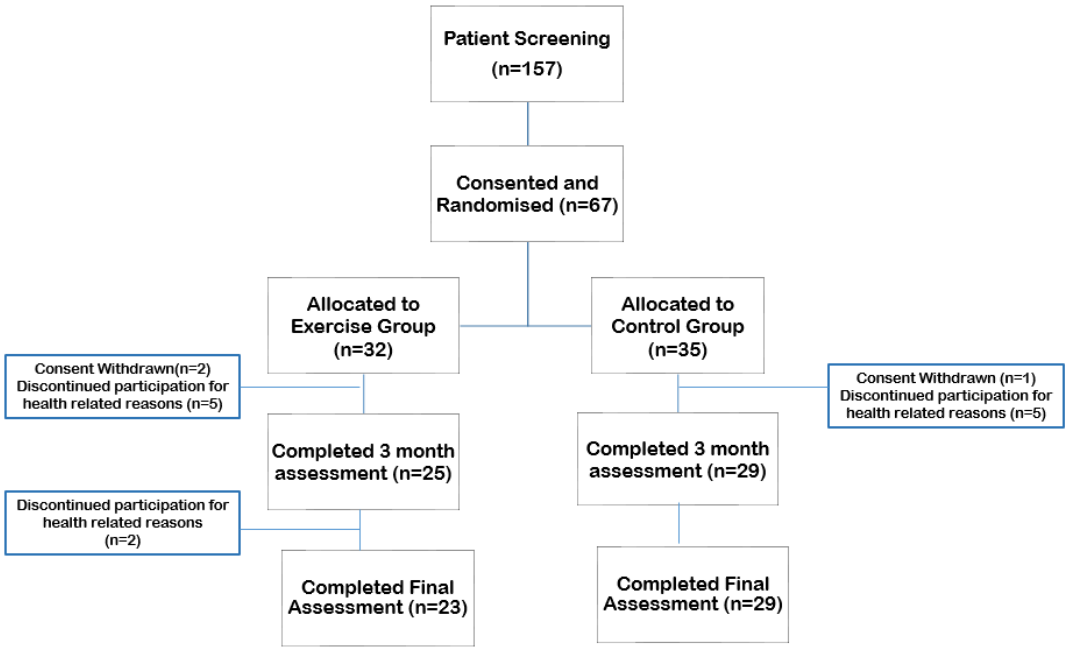


Figure 23 ExPeCT Trial Flowchart

2014	n=4	n=4 SJH
2015	n=28	n=8 SJH n=20 Guy's Hospital
2016	n=27	n=11 Tallaght Hospital n=4 Mater Hospital n=1 Beaumont Hospital n=1 St Luke's Hospital n=10 Guy's Hospital
2017	n=8	n=1 Tallaght Hospital n=7 Guy's Hospital

Table XX: Number of patients recruited to ExPeCT at each site.

Patient characteristics are presented in Table XX. Groups were comparable at baseline for demographic characteristics with the exception of number of smokers, which was significantly higher in the exercise group. Patients were on average 69.4±7.3 (s.d.) years of age with a BMI of 29.2±5.8 kg/m^2. Half of the patients were either overweight (n=15, 22%) or obese (n=19, 28%). Most participants were married, lived with a partner and were retired.

		Study Arm		
Characteristic	**Total Study Population**	**Exercise Arm (n=33)**	**Control Arm (n=38)**	**P Value**
Age (years ± s.d.)	69.4 ± 7.3	69.8 ± 6.97	69.5 ± 7.65	.894
BMI (Kg/m^2 ± s.d.)	29.2 ± 5.8	28.4 ± 4.84	29.86 ± 6.95	.589
Waist Circumference (cm ± s.d.)	102 ± 35.2	100.5 ± 14.62	104.0 ± 22.32	.109
Systolic Blood Pressure (mean mm Hg ± s.d.)	139.35 (23.34)	141.07 (16.57)	136.17 (14.18)	.400
Diastolic Blood Pressure (mean mm Hg ± s.d.)	78.67 (9.91)	78.37 (8.52)	78.70 (11.47)	.427
Time Since Cancer Diagnosis (Months, median (IQR))	54 (6.75-84.0)	64 (6.75- 87)	47.6 (7.25-84)	.863
Current Smoker, n (%)	5 (8)	5 (8)	0 (0)	.012
Marital Status, n (%)				
Married	37 (61)	15 (25)	22 (36)	.134*
Widowed	11 (18)	8 (13)	3 (5)	
Divorced/Separated	9 (15)	6 (10)	3 (5)	
Never Married/Not answered	4 (7)	1 (2)	3 (5)	

Work Status n (%)				
Currently employed	7 (11)	2 (3)	5 (8)	.180*
Retired	49 (80)	24 (39)	25 (41)	
Disability/Unemployed	2 (3)	4 (7)	0 (0)	
Living Arrangement, n (%)				
Alone	13 (21)	8 (13)	5 (8)	.359*
With Partner	39 (64)	16 (26)	23 (38)	
With Other Family	7 (11)	5 (8)	2 (3)	
Other	2 (3)	1 (2)	1 (2)	
Ethnicity, n (%)				
White/Caucasian	59 (91)	27 (44)	32 (52)	.823*
Black/Afro-car	4 (6)	2 (3)	2 (3)	
Asian	2 (3)	1 (2)	1 (2)	

Table XXI Demographic Characteristics at Baseline

s.d.: Standard Deviation, IQR: Inter Quartile Range

*p value from $\chi 2$ test, other p values from t test.

Medical characteristics are presented in Table XXI. At baseline, physical activities levels were comparable in both groups. Patients had extensive metastatic bone disease characterised by >2 regions affected by metastatic lesions (Table XXI). Groups were comparable at baseline for disease characteristics with the exception of numbers of number of patients actively receiving radiation therapy at baseline, which were significantly higher in the exercise group.

		Study Arm		
Characteristic	**Total Study Cohort**	**Exercise Arm (n=33)**	**Control Arm (n=38)**	**p Value**
Comorbidity, n (%)				
Hypertension	32 (52)	17 (28)	15 (25)	.517
Hypercholesterolemia	26 (43)	12 (20)	14 (23)	.684
Diabetes	15 (25)	7 (11)	8 (13)	.766
CV Disease	13 (21)	8 (13)	5 (8)	.176
Severity of Bone Metastatic Disease, n (%)				
Minor (1 region affected)	27 (44)	12 (20)	15 (25)	.692#
Moderate (2 regions affected)	11 (18)	6 (10)	5 (8)	
Major (>2 regions affected)	23 (38)	10 (16)	13(21)	
Gleason score, n (%)				
7	7 (11)	3 (5)	4 (7)	.934#

8	22 (36)	11 (18)	11(18)	
9	24 (39)	11(18)	11(18)	
Unknown	8 (13)	5 (8)	3 (5)	
Primary treatment, n (%)				
Hormones only	41 (67)	22 (36)	19 (31)	.246
Radiation Only	6 (10)	0	6 (10)	.011
Hormones + Radiation	8 (13)	5 (8)	2 (3)	.412
Unknown	6 (10)	3 (5)	3 (5)	-
Achieving Aerobic Physical Activity Guidelines, n (%)				
Yes	32 (54)	17 (28)	15 (25)	.73
No	28 (46)	12 (20)	16 (26)	
Overall physical activity level (MET-h/week; mean ± s.d.)	36.95 ± 53.94	36.26 ± 42.70	37.63 ± 63.41	.824
Overall daily sedentary activity levels (mins ± s.d.)	273.70 ± 260.85	270.74 ± 248.4	276.38 ± 275.29	.347

Table XXII Medical Characteristics at Baseline

s.d.: Standard Deviation, MET: Metabolic Equivalent

(n=61 included), $^{\#}$p value from $\chi 2$ test, other p values from t test.

6.3.2. Intervention Adherence

Of the 33 participants in the exercise group, 26 (79%) completed the 3 month supervised exercise programme, and 24 (73%) completed the 6 month intervention. Overall adherence to the supervised sessions was 83% (329 out of 396 sessions attended). Pain, shortness of breath and conflicting medical appointments were the most common reasons given for missed sessions. Participants were adherent to both the intensity (82%) and duration (83%) of the prescribed exercise programme during class sessions. Patients attended on average 10.41 (s.d.= 3.62) out of 12 supervised exercise sessions. Overall adherence to the non-supervised home exercise sessions was 72% in the first three months (patients recorded the prescribed aerobic exercise intensity and duration in their log books). Participants were equally adherent to both the intensity (74%) and duration (71%) aspects of the prescribed home exercise programme during months 1-3. During the last three unsupervised months of the programme, adherence to the home exercise programme was 67%. Similar to the first three months of the study, participants reported similar adherence levels for both the intensity (69%) and duration (65%) of the

prescribed home exercise programme. Exercise adherence levels in the intervention group did not correlate with patient-reported outcomes at month 3 or month 6.
No adverse events were reported by participants enrolled in this study.

6.3.3. Physical Activity and Sedentary Behaviour

Physical activity levels were comparable between exercise and control participants at baseline (p=0.59). There was no change in physical activity levels of either group from baseline to 3 months (β = -6.22, s.e. = 8.49, p=0.46) or from baseline to 6 months (β = 2.13, s.e. = 8.54, p=0.80). Similarly, sedentary behaviour was comparable between groups at baseline (p=0.38). There was no change in sedentary behaviour of either group from baseline to 3 months (β = -20.63, s.e. = 44.89, p=0.65) or from baseline to 6 months (β = -81.31, s.e. = 45.03, p=0.07).

At baseline, 32 of the 67 (48%) participants were meeting the current ACSM exercise guidelines for patients living with cancer, measured by the Harvard Health Professionals Physical Activity self-report tool (150 minutes moderate to vigorous intensity exercise per week). The percentage of participants in the exercise group meeting exercise guidelines increased from 58% and 57% at months 0 and 3 respectively, to 66% at 6 months. The percentage of participants in the control group meeting the physical activity guidelines did not change over time (48% at baseline, 50% at month 3 and 48% at month 6).

6.3.4. Intervention effects on Sleep, Stress and Depression

The mean sleep scores at baseline were 6.77 (s.d.=3.93) and 7.03 (s.d.=3.90) in the control and exercise groups, respectively. Groups were comparable at baseline (p=0.61), 3 months (p=0.95) and at 6 months (p=0.81) (Table XXII). There were no significant changes in sleep scores from baseline to 3 months (p=0.15), or baseline to 6 months (p=0.47) (Table XXIII). The mean stress scores at baseline were 2.86 (s.d.=3.43) and 3.74 (s.d.= 2.82) in the exercise and control groups, respectively. Groups were comparable at baseline (p=0.813), 3 months (p=0.27) and 6 months (p=0.76) (Table XXII). There were no significant changes in stress scores from baseline to 3 months (p=0.098), or baseline to 6 months (p=0.81) (Table XXIII). Similarly, depression scores at baseline were 4.43 (s.d.=5.17) and 2.96 (s.d.=4.09) in the exercise and control groups, respectively. Groups were comparable at baseline (p=0.29), 3 months (p=0.19) or 6

months (p=0.27) (Table XXII), however when changes were examined over time, the exercise group experienced a significant decrease in depression scores between baseline and 3 months when compared to the change experienced by the control group (p=0.02, Table XXIII).

6.3.5. Intervention effects on Quality of Life

At baseline, the mean overall quality of life scores were 121.3 (s.d.=21.16) and 119.49 (s.d.=20.73) for the exercise and control groups, respectively. Groups were comparable at baseline (p=0.50), 3 months (p=0.73) and 6 months (p=0.99) (Table XXII). There were no significant changes in stress scores from baseline to 3 months (p=0.87), or baseline to 6 months (p=0.66) (Table XXIII).

	Baseline			Third Month					Sixth Month				
Outcome by group	n	Mean	s.d.	n	Mean	s.d.	Difference between groups (95% CI)	p-value	n	Mean	s.d.	Difference between groups (95% CI)	p-value
Sleep													
Exercise Group	30	7.03	3.90	25	6.40	4.21	0.07 (-2.09: 2.23)	0.95	23	6.78	4.94	0.30 (-2.20; 2.81)	0.81
Control Group[#]	31	6.77	3.93	27	6.33	3.54			25	6.48	3.63		
Stress													
Exercise Group	29	2.86	3.43	25	3.48	2.87	-0.91 (-2.57; 0.74)	0.27	23	3.30	3.14	0.26 (-1.47; 2.00)	0.76
Control Group[#]	31	3.74	2.82	28	4.40	3.12			25	3.04	2.85		
Depression													
Exercise Group	30	4.43	5.17	25	3.28	4.66	1.31 (-0.67; 3.33)	0.19	23	3.56	4.99	1.29 (-1.04; 3.64)	0.27
Control Group[#]	31	2.96	4.09	28	1.96	2.25			26	2.27	3.01		
Quality of Life													
Exercise Group	29	121.3	21.16	25	120.16	18.06	-1.89 (-12.79; 9.01)	0.73	23	122.99	23.28	0.01 (-13.25; 13.27)	0.99
Control Group[#]	30	119.4	20.73	28	122.05	21.11			26	122.98	22.81		
Memory													
Exercise Group	29	0.72	1.07	25	.88	1.39	-0.08 (-0.69; 0.53)	0.80	23	1.04	1.7	0.12 (-0.94; 0.77)	0.84
Control Group[#]	30	0.80	1.27	28	.96	1.66			26	0.92	1.5		

Table XXIII Intention-to-treat analysis: mean and s.d. values and outcome differences between both groups at baseline and at third and sixth months according to the general linear model

CI: Confidence Interval, s.d.: Standard Deviation
[#]Control Group is reference group

Variables	Beta	s.e.	p-value
Sleep			
Group (Exercise vs Control)	0.16	0.93	0.87
Time			
Baseline	Reference		
3 months	-0.53	0.37	0.15
6 months	-0.28	0.38	0.47
Stress			
Group (Exercise vs Control)	-0.60	0.65	0.35
Time			
Baseline	Reference		
3 months	0.58	0.35	0.10
6 months	-0.09	0.36	0.81
Quality of Life			
Group (Exercise vs Control)	-1.04	5.29	0.84
Time			
Baseline	Reference		
3 months	-0.28	1.75	0.87
6 months	0.78	1.80	0.66
Depression			
Group (Exercise vs Control)	1.05	0.99	0.29
Time			
Baseline	Reference		
3 months	-1.03	0.43	0.02
6 months	-0.62	0.44	0.15
Memory			
Group (Exercise vs Control)	-0.02	0.34	0.97
Time			
Baseline	Reference		
3 months	0.17	0.14	0.21
6 months	0.12	0.14	0.16

Table XXIV Results of the generalised linear model regarding the effects of exercise on Sleep, Stress, Quality of Life and Depression over time

(n=61)

CI=Confidence Interval, s.e, Stadard Error

*Control group is reference group

6.3.6. Cardiovascular Measures

Descriptive statistics for cardiovascular measures at each assessment (baseline, 3 months and 6 months) are shown in Table XXIV. Measures of systolic and diastolic blood pressure were also comparable between groups at baseline (p=0.40 and p=0.89 respectively). Systolic blood pressure was significantly lower in the exercise group when compared to the control group at 3 months (p=.008) and 6 months (p=.011). Similar results were seen for diastolic blood pressure at 3 months and 6 months, however these differences did not reach statistical significance (Table XXIV). Measures of BMI and waist circumference were comparable between groups at baseline, 3 months and 6 months.

		Baseline			**3 months**			**6 months**		
Outcome	Group	Mean	s.d.	p-value	Mean	s.d.	p-value	Mean	s.d.	p-value
SPB	Exercise	141.07	16.57	.400	131.14	12.97	.008	131.11	13.77	.013
	Control	136.17	14.18		142.48	15.39		144.66	18.64	
DBP	Exercise	78.37	8.52	.899	76.63	6.76	.306	76.57	8.32	.225
	Control	78.70	11.47		79.04	9.11		79.62	7.17	
BMI	Exercise	28.45	4.85	.213	28.47	4.93	.373	28.61	4.83	.406
	Control	29.93	4.30		29.65	4.36		29.81	4.78	
Waist Circumference	Exercise	100.5	14.62	.298	100.06	12.34	.481	101.20	11.15	.891
	Control	104.13	11.73		102.52	12.15		101.67	12.01	

Table XXV Differences in control and exercise group measures at baseline, 3 months and 6 months

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, s.d.: Standard Deviation

6.4. Discussion

This study demonstrated that a six month aerobic exercise intervention did not significantly improve health related quality of life in patients with metastatic prostate cancer. In addition, the six month exercise intervention did not result in significant improvements in symptoms of stress or sleep quality. The exercise intervention was tolerated well by a group of patients with a high burden of metastatic prostate cancer, and paves the way for future exercise studies involving this patient group.

The ExPeCT Trial builds on previous work which has demonstrated that physical activity programmes are well-tolerated by patients with metastatic bone disease (Galvao *et al.*, 2017). This is demonstrated by the high attendance and compliance of patients living with an extensive disease burden. The ExPeCT adherence rate is higher than the values reported in exercise interventions involving patients receiving chemotherapy and is also within the common range reported by trials involving older adults without cancer (Courneya *et al.*, 2007). The findings support the current evidence that reports interventions that combine the supervision of exercise training in tandem with a requirement of independent exercise are likely to promote good adherence (Bourke *et al.*, 2013). Additionally, the level of adherence to the exercise programme was maintained in the 3 month unsupervised exercise periods demonstrating that patients when started on the programme were able to continue exercising with minimal input at home. The dropout rate in the ExPeCT trial is in line with the rate found in a recent study of patients with metastatic prostate cancer, but lower than other studies involving patients with advanced disease (Temel *et al.*, 2009, Quist, 2013, Galvao *et al.*, 2017). The systematic review presented in Chapter 3 identified progression of disease status as the main cause for dropout during exercise interventions, which is consistent with the experience of the ExPeCT trial. It may be possible that in the context of advancing disease, those in the exercise group were more challenged than those in the control group and were therefore more likely to drop out.

Treatment and disease-related side effects as well as fear of skeletal fracture are likely to reduce physical activity levels in patients with bone metastatic prostate cancer. However, similar to previous studies, this trial has demonstrated that patients living with metastatic disease reported higher levels of self-report physical activity levels at baseline then patients with early stage disease, 48% in the ExPeCT trial compared to previous levels of 21% in patients with localised disease (Galvão *et al.*, 2015). The recruitment rate or baseline activity levels reported in ExPeCT might also suggest that we have recruited a sample of atypical men with advanced prostate cancer. This may be the case, given the relative wellness indicated in baseline patient reported outcomes and higher levels of baseline physical activity levels then previous studies of metastatic prostate patients (Zopf *et al.*, 2017). Patients recruited for the ExPeCT trial may already have an interest in exercise and had higher baseline levels of activity compared to those not interested in exercise. This is important as it may result in an underestimation of the potential benefits of exercise in this population. As in previous trials, it may be those who suffer the most from side effects of cancer or cancer treatment who benefit the most

from physical activity interventions. The ExPeCT trial did not exclude patients based on baseline physical activity levels. Future trials exploring the effects of exercise specifically in sedentary patients are warranted. Future exercise trials that include all patients with metastatic disease, including those who are sedentary at baseline, are needed. This will ensure that the results of trials reflect advanced cancer populations found in the clinical setting.

As outlined in Chapter 1, physical activity interventions can improve health related quality of life in advanced cancer populations. The patient population in the ExPeCT trial exceeded the quality of life scores reported in normative data of male patients living with cancer (Penny *et al.*, 2005). The absence of changes in measurements of quality of life used in ExPeCT may be due to a number of factors. Importantly, the FACT-P was not created for patients with advanced cancer, and may not be able to detect differences between patients with this additional symptom burden. A quality of life measure such as the McGill Quality of Life Questionnaire may have been more appropriate for the ExPeCT study when compared to a prostate cancer specific measure. Another possible explanation for this finding are the high scores reported by this population at baseline. It is most likely that a ceiling effect was reached with these patients, possibly due to a prolonged treatment regime and ongoing medical follow-up, reported in previous studies involving patients living with cancer (van de Poll-Franse et al., 2006, Wong et al., 2015). Patients living with cancer may be satisfied with their 'survival status' and score high in all quality of life questionnaires despite existing limitations and complaints (Montazeri, 2009). Furthermore, given the complexity of quality of life in patients living with metastatic disease, exercise may have had limited effects on quality of life. Many uncontrollable factors influence quality of life during advanced cancer, and a global measure of cancer-specific quality of life may be too broad to detect the likely narrower effects of exercise training (Galvao *et al.*, 2017). There is a possibility that the active participants enrolled in the ExPeCT trial had greater self-efficacy levels then the general metastatic prostate cancer population, and therefore reported higher self-report scores for measures of quality of life. Post-diagnosis recreational physical activity is associated with better physical quality of life in non-metastatic prostate cancer survivors (Farris *et al.*, 2017). The literature regarding the effect of exercise on quality of life in patients with advanced cancer is inconsistent. While improvements in quality of life scores have been reported (Rief *et al.*, 2014), the majority of papers report no change in outcomes (Cormie *et al.*, 2013a, Ligibel *et al.*, 2016). Future trials in advanced cancer populations should give careful consideration to the choice of quality of life outcome.

Clinically, the involvement of patients with metastatic cancer in exercise programmes may have considerable implications for patients' overall health. Observational evidence suggests that men with prostate cancer undergoing ADT are at an increased risk of developing cardiovascular disease (Levine *et al.*, 2010). Reducing diastolic blood pressure by 5mm Hg or systolic blood pressure by 10mm Hg could reduce the risk of coronary heart events by 22% and stroke by 41% (Law *et al.*, 2009). The ExPeCT intervention group experienced a 10mm Hg decrease in blood pressure at 3 months. Importantly, this was maintained at 6 months. Conversely, the control group experienced increases in both systolic and diastolic blood pressure over the six month intervention, emphasising the important role exercise can play in attenuating the side effects of ADT, and managing cardiovascular risk in men receiving hormone therapy. This has previously been demonstrated in populations with early stage prostate cancer (Culos-Reed *et al.*, 2010), however patients living with metastatic prostate cancer can receive ADT for long periods of time, and therefore may respond more favourably to exercise than those with short-term ADT exposure. This has previously been the case with outcomes such as muscle performance and body composition (Taaffe *et al.*, 2018). The potential role of exercise in managing cardiovascular risk in patients receiving ADT warrants further investigation in larger populations of patients living with advanced prostate cancer.

In accordance with other exercise trials in localised prostate cancer and metastatic cancer (Segal *et al.*, 2003, Galvao *et al.*, 2017), there were no changes in any of the anthropometric variables (BMI, weight, or waist circumference) measured in the ExPeCT study. As discussed in Chapter 2, quantification of changes in body composition by using BMI and girth measurements is difficult, and more precise measures, such as dual energy X-ray absorptiometry (DEXA) or MRI are preferable to assess changes (Bourke *et al.*, 2013). Indeed, a 12 week combined resistance and aerobic exercise intervention, with whole body and regional lean mass as primary endpoints, resulted in improvements in skeletal muscle mass via DEXA scanning in non-metastatic patients with prostate cancer (Galvao *et al.*, 2010). The efficacy of lifestyle interventions for evoking changes in body composition is important, as higher levels of body fat have been associated with higher grade tumours and disease progression (Amling *et al.*, 2004). Future studies should assess these parameters in metastatic populations by using precise anthropometric measurement techniques.

6.4.1. Strengths and Limitations

The current study has several strengths and limitations worthy of comment. Firstly, this is one of the largest RCT's evaluating the effects of exercise in prostate cancer patients with bone metastases or in any other cancer group with bone metastatic disease. The approach to exercise prescription in this study was patient inclusive, such that all patients can be prescribed some amount of exercise despite the presence of metastases. This method has significant potential for use in the clinical setting and adds to the recent paradigm shift in relation to exercise prescription in advanced prostate cancer (Galvao et al. 2018). A strength of the current study is the objective measurement of adherence to the physical activity intervention in this metastatic population. Objective monitoring is a valid tool for assessing physical activity and motivating physical activity adherence (Koizumi *et al.*, 2009). This dual purpose, as well as the potential for objectivity, support the use of accelerometers for optimising the health benefits of physical activity after a cancer diagnosis (Rogers, 2010). Certainly, in this study, the objective monitoring of participant adherence may have resulted in the high adherence rates observed in this study, which are in line with the adherence rates found in randomised controlled trials of early stage prostate cancer patient participating in 12-week exercise interventions (Segal *et al.*, 2003). In contrast to the factors found to predict adherence in early stage prostate cancer patients, such as hormonal symptoms, ExPeCT participants reported pain and shortness of breath as the most common physical reasons for missed sessions. These symptoms of advanced cancer may be the most crucial factors to consider for patients with advanced stages of prostate cancer (Craike *et al.*, 2016). Additional factors for missing sessions commonly included conflicting medical appointments, reported previously in exercise trials involving metastatic prostate cancer patients (Galvao *et al.*, 2017). Although adherence to the exercise intervention was very good, it was not optimal. As in studies with early prostate cancer patients, further work to identify factors that influence adherence in advanced prostate cancer is needed, as this will have important implication for maximising adherence during clinical trials of exercise interventions (Courneya *et al.*, 2004).

There are a number of limitations to this study which warrant discussion. The recruitment pathway for patients with advanced cancer is challenging and relies on referral from oncologists. A potential selection bias associated with referral patterns by the nurses and oncologists may have influenced the results by selecting people who were initially more motivated to perform physical activities (Coats *et al.*, 2013). This highlights the challenges of implementing rehabilitative interventions in clinical practice. Additionally,

this study was ancillary to a larger RCT which required multiple blood draws, which may have affected participant numbers. Fatigue, a dominant prostate cancer symptom and the most common adverse event resulting from mCRPC treatment, was not measured in the current study (Sternberg *et al.*, 2013). This is significant, as the symptoms and side effects of advanced cancer and associated treatments, such as fatigue, may have had a significant role on quality of life scores. Additionally, current evidence suggests that resistance training is associated with clinically important positive effects on muscular function and body composition in patients during treatment or in long-term follow-up (Strasser *et al.*, 2013). A clinically meaningful change in FACT-P is estimated to be between 6 and 10 points (Cella *et al.*, 2009), and a significant difference between intervention and control groups (mean diff $\Delta = 5.3$) was previously reported following a 12 week programme of resistance exercise in men with prostate cancer receiving androgen deprivation therapy for at least three months (Segal *et al.*, 2003). The aerobic intervention in the ExPeCT trial was not prescribed to target gains in these measures, however the inclusion of resistance training may have resulted in improved outcomes post-intervention. Finally, participants with any level of physical activity levels were included in this study which may have resulted in a sample not representative of the general advanced prostate cancer population.

6.5.Conclusion

This study supports the safety and feasibility of exercise interventions in metastatic populations. Contrary to the study hypotheses, aerobic exercise did not significantly improve cancer-specific quality of life in men with metastatic prostate cancer. Further work is needed to investigate the benefits associated with exercise interventions for patients living with advanced prostate cancer.

7. Chapter 7: Discussion

7.1. Introduction and Main Findings

The benefits of exercise for people living with cancer are well established (Chapter 1). In advanced disease, there is a need to examine the potential physical and psychological benefits of engaging in physical activity. The aim of this thesis was to explore the role of physical activity for people living with advanced stages of cancer using quantitative and qualitative methods. The use of both a quantitative and qualitative element in this work enabled one method of investigation to inform the other. For example, the views of health professionals towards exercise in advanced cancer, outlined in Chapters 5a and 5b, informed the research teams approach to patient recruitment for Chapter 6. This approach enabled a thorough examination of the outcomes associated with exercise in advanced cancer, while also allowing an exploration of the perceptions of patients and healthcare professionals. The main findings of this thesis are outlined in the following sections.

A narrative review examining exercise prescription to patients with bone metastases (Chapter 1) found that exercise interventions for patients with bone metastases are associated with positive physical and self-reported outcomes. Studies reporting adverse events did not find a high fracture incidence with exercise in comparison with control participants, or an association between exercise and fracture risk; however, the need to individualize exercise prescription and adapt exercises to patient ability were reinforced in all papers reviewed. While exercise prescription to patients with bone metastases does involve complex decision making, a number of tools (e.g fracture risk assessment tools (FRAX) and pain inventories (BPI)) are available that may inform both patient assessment and exercise prescription. A systematic review of exercise trials involving patients with advanced cancer (Chapter 3) found that recruitment (mean 49% (SD = 17; range 15-74%), adherence (range 44-95%) and attrition rates (mean 24% (SD = 8; range 10-42%) varied widely among the studies reviewed. Additionally, definitions and the measurement of exercise adherence varied widely. With increasing evidence supporting the safety and efficacy of exercise training in patient with advanced and complex presentations, concentrated efforts are needed to increase the numbers of patients with advanced disease, including those with metastatic disease, recruited to exercise programmes and to ensure patients recruited are representative of clinical practice.

Further studies in this thesis (Chapters 5a and 5b) concluded that clinicians and physiotherapists feel that physical activity is safe and important in the advanced cancer

patient cohort. However, both groups demonstrated a need for further information in the area of physical activity and advanced disease. Similarly, patients expressed a need for further information regarding physical activity following diagnosis (Chapter 4). Some of the challenges of implementing this into clinical practice were highlighted by clinicians and physiotherapists, who reported many concerns regarding physical activity in the advanced cancer population. These concerns centred on a risk of pathological fracture and a risk of spinal cord compression. Patients were perceived by physiotherapists as highly susceptible to injury due to their advanced stage of disease. This is a significant issue for patients with advanced stages of disease. There is, however, evidence that carefully designed physical activity programmes can be safely introduced for patients with many symptoms of advanced disease, including bone metastases (Chapter 1). Many patients in Chapter 4 reported a decrease in physical activity levels following a diagnosis of advanced cancer and did not identify common 'cues to action' post-diagnosis that prompted them to maintain or increase their physical activity level, such as written information about physical activity or referral for exercise consultations. This issue was also highlighted by physiotherapists in Chapter 5a, who felt patients with advanced cancer have limited exposure to factors that may prompt the maintenance or an increase in physical activity levels. There is a need to increase 'cues to action' or prompts which encourage patients with advanced cancer to engage in physical activity. These cues to action may take the form of verbal prompts from healthcare staff to encourage physical activity or visual cues such as pamphlets or posters which focus on the benefits of physical activity. Recent evidence on the benefits of physical activity for patients with advanced disease should be disseminated widely to healthcare professionals. This may encourage both discussion around exercise during hospital consultation and the introduction of exercise rehabilitation referrals as a part of the standard care of patients with advanced cancer.

If a risk of fracture is perceived as a barrier to exercise, tools to stratify risk of fracture can be used, as detailed in Chapter 1. For example, Mirels' classification system for impending pathologic fracture is a valid screening tool for metastatic lesions in long bones (Jawad and Scully, 2010). Resistance programmes were not encouraged by physiotherapists in Chapter 5a due to fear of pathological fractures. Despite this, recent studies have shown very promising results in trials involving resistance exercise programmes for patients with metastatic disease. A randomised control trial involving 12 weeks of adapted resistance training in an advanced prostate cancer population resulted in no adverse effects or increase in pain (Cormie *et al.*, 2013). Educational efforts targeting fears and misconceptions about the prescription of physical activity for patients

with advanced disease may help to improve physiotherapists' and clinicians confidence in recommending physical activity to this population. A previous health professional education programme, introduced to encourage discussions between nurses and patients living with cancer, found that a 60 minute exercise medicine education session significantly improved delivery of very brief physical activity advice delivered to patients ($Z = -4.39$, $p \leq 0.01$) (Webb *et al.*, 2016). Additionally, a systematic review of physical activity education programmes delivered to trainee physicians demonstrated improvements in physical activity counselling knowledge and skills associated with the delivery of physical activity education (Dacey *et al.*, 2014). Educational efforts targeted at healthcare professionals, both in-training and in-practice, may positively influence future physical activity education delivered to patients living with cancer in Ireland.

A number of barriers to engaging patients with advanced disease in physical activity are identified in Chapters 3 and 4. Firstly, narrow inclusion criteria for exercise clinical trials restricts the number of patients with advanced cancer who are eligible for studies involving physical activity interventions. Inclusion criteria often includes narrow prognostic criteria or measures of functional performance, excluding many patients with advanced cancer. Broadening inclusion criteria may increase recruitment rates to physical activity programmes. This would ensure patients recruited represent the advanced cancer population found daily in clinical practice. Additionally, although patients did not report a cancer diagnosis as a barrier to physical activity, many symptoms of advanced disease, such as pain and fatigue, were identified as barriers to these patients participating in physical activity (Chapter 4). Referral to an exercise specialist should be considered for these patients. Exercise specialists can prescribe tailored physical activity programmes which consider patients' individual barriers to exercise. Individualised exercise programmes would accommodate transient changes and fluctuations in a patient's wellbeing through-out courses of treatment and through-out their disease progression (Hart *et al.*, 2017). Indeed, the ExPeCT Trial (Chapter 6) introduced an individualised exercise programme for patients with metastatic prostate cancer. This trial demonstrated that a progressive aerobic exercise programme can be introduced to patients living with metastatic prostate cancer in a multicentre setting. Although the results of the programme did not result in significant changes in psycho-social self-report measures, the exercise intervention was well tolerated by participants and did not result in any adverse events, laying the foundation for further trials in this population.

7.2. Analysis of key points

There are a number of key points raised by the work in this thesis which will be discussed below.

7.2.1. Exercise Oncology Education and Healthcare Professionals

Studies in this thesis (Chapters 5a and 5b) demonstrate that both physiotherapists and clinicians felt they needed further education regarding the role of physical activity for patients with advanced cancer. Studies found that despite enthusiasm for exercise engagement in the oncology setting, there are concerns over exercise prescription to patients with complex presentations, such as bone metastases. This reflects existing literature in this area, describing an impression among clinicians that exercise may increase the risk of injury, fatigue, and exacerbation of symptoms in the patient (Blanchard *et al.*, 2004, Demark-Wahnefried *et al.*, 2005). A study examining barriers to discussing exercise to people with cancer in clinical practice found 33% of clinicians did not feel qualified to discuss exercise or refer to an exercise program (Nadler *et al.*, 2017). However, the most important facilitator clinicians could identify, to encourage discussions around exercise with patients, was clinician education sessions (48%). There is a need to disseminate the evidence on the benefits of physical activity for patients living with cancer to healthcare professionals. Education sessions for health professionals should focus on the existence and practical implementation of physical activity guidelines and provide information on the safety of exercise.

It is known that prostate cancer survivors need long-term information support, including strategies such as exercise, to improve long term recovery from cancer (Bernat *et al.*, 2016). Patients seek guidance from their healthcare professionals regarding this information support. Patient reported barriers to engagement in exercise include lack of knowledge on how to exercise and a lack of specific advice or referral from their healthcare team (Peeters *et al.*, 2009). The lack of discussion between patients and physicians about exercise highlights an important and actionable gap in current practice (Alibhai et al., 2006). To embed exercise into the clinical care model, further education is needed for clinicians and other health professionals involved in the care of patients diagnosed with cancer to increase conversations around exercise with patients.

Despite obstacles to implementation, evidence from more than eighty controlled exercise trials demonstrates that the oncologic community must strive to include exercise in cancer care (Santa Mina *et al.*, 2012). The American Cancer Society guidelines for

prostate cancer survivorship advises primary care clinicians to educate survivors regarding the association between physical activity and lower overall and prostate cancer-specific mortality and improved health related quality of life (Skolarus *et al.*, 2014). Studies in this thesis found a high level of agreement that exercise counselling should be a component of care. A targeted gradual approach, encouraging education and multi-disciplinary integration at defined stages across the cancer pathway, is recommended to facilitate future practice change (Granger *et al.*, 2018). The specific information needs of clinicians in areas of oncology practice should be identified and efforts made to address these needs with the necessary education delivered by exercise specialists in oncology.

7.2.2. Recruitment of Patients with Advanced Cancer to Exercise Trials

While momentum for exercise training in patients with bone metastases is increasing in the research arena, clinically, our experiences with recruitment to the ExPeCT clinical trial highlighted that clinicians harbour concerns regarding exercise prescription in this cohort. Participant recruitment was challenging and resulted in the ExPeCT Trial not meeting its accrual target (Sheill *et al.*, 2017). This is an important finding that needs further attention. It is widely acknowledged that recruitment difficulties can lead to RCTs requiring considerable additional research resources in extensions or taking so long that their interventions become outdated (Donovan *et al.*, 2016). Difficulties with recruitment may also have implications for the generalisability of the findings of ExPeCT. Initially it was planned to open the trial in two Irish centres; however, after slow recruitment over the initial four months, this was expanded to five Irish centres. Successful recruitment of participants is critically dependent on factors such as administrative support, attitude of clinical staff, volume/turnover of patients, realistic study protocols, and stability of the patient population (Kadam *et al.*, 2016). Where possible, all of these factors were given great consideration by the research team in order to optimise recruitment. For example, difficulty with recruitment may have been experienced as the ExPeCT trial involved an exercise intervention. Exercise interventions are not a part of the standard care offered to patients diagnosed with cancer in Ireland, particularly to those with more advanced stages of disease. Therefore, a number of organisational challenges existed when inviting all patients with advanced prostate cancer, and metastatic disease in particular, onto this exercise trial. Clinical staff required information about the exercise intervention, in order to approach patients and provide accurate and appropriate information. To ensure health professionals were comfortable recruiting to an exercise trial, the research

team gave presentations to medical teams in palliative care, medical and radiation oncology outlining the positive outcomes associated with exercise after a cancer diagnosis. Members of the ExPeCT research team attended clinics of urology and medical oncology doctors to screen patients for the ExPeCT trial. In addition, presentations were given to allied health professionals to encourage greater awareness of the role of exercise for patients with metastatic cancer. Many patients refused participation in the ExPeCT trial due to the exercise component. Further work is necessary in order to highlight the benefits of participating in exercise trials to the advanced cancer group. The recruitment rate in the ExPeCT trial (43%) was lower than the mean recruitment rate found in the systematic review of exercise trials in advanced cancer (Chapter 3). Although it is higher than recruitment rates of 15% found in the first studies in the advanced cancer population (Lowe *et al.*, 2009), recruitment rates in the advanced cancer population can be as high as 74% (Oldervoll *et al.*, 2011). In the latter trial patients were referred directly from an oncologists, highlighting the need for clinician involvement in the recruitment process.

Valuable lessons were learned about co-ordinating the recruitment of patients from multiple centres to ExPeCT. Commonly acknowledged organisational/logistical challenges were reported by the research and clinical staff recruiting to the ExPeCT trial, including unexpectedly lower numbers of eligible patients, strong patient preferences for particular interventions, and patients seemingly unwilling to consider randomisation (Mc Daid *et al.*, 2006). Recruitment strategies used in ExPeCT were labour intensive and required much time dedicated to the process of screening medical notes and assessing eligibility, emphasising the importance of human resources for future trials. Research teams involved in any future trials involving exercise should engage with clinical trials nurses regularly throughout the recruitment period to answer questions regarding patient eligibility for exercise and answer any queries regarding the exercise intervention. A pilot trial of the ExPeCT study may have been helpful in determining the recruitment feasibility and may have ensured the recruitment of participants was more effective and efficient. Despite this, a number of recruitment barriers were addressed during the course of the ExPeCT trial, paving the way for future exercise trials involving metastatic populations.

7.2.3. Cancer Survivorship and Exercise Services in Ireland

Physicians responding to the survey in Chapter 5b commented on the lack of exercise prescription services available for patients living with cancer, and the need for a mechanism to prescribe exercise in the clinical setting. Advances in early detection and treatment of cancer and the aging population mean that 1 in 20 Irish people will be a cancer survivor by 2020 (Department of Health, 2017). There has been increasing awareness of cancer survivorship in the recent National Cancer Strategy, and awareness of long-term health issues related to cancer and its treatment is improving (Demark-Wahnefried *et al.*, 2005, Stein *et al.*, 2008). The growing number of patients diagnosed with cancer, and the increased length of survival, is a challenge for health care policy and delivery in Ireland. To meet this challenge, there is a need to develop a model of care delivery to maximize the health and well-being of survivors of cancer. This should focus on factors such as effective symptom management, prevention of late effects, and health promotion. Exercise services are well positioned to target these factors. However, referral to exercise specialists is not a part of the standard care received by oncology patients in Ireland. Irish cancer survivors have identified a striking lack of contact with health professionals that might be influential in facilitating recovery and rehabilitation (Ivers, 2009). The rehabilitation services available for patients living with cancer does not reflect the established body of evidence in this area. In contrast, the American College of Surgeons Commission on Cancer produced a standard that all accredited institutions provide cancer rehabilitation services, which has spurred healthcare providers in the USA to develop cancer rehabilitation programmes across diverse delivery settings (Surgeons, 2016). Plans for improved survivorship care are being developed and implemented internationally, including the recent American Cancer Society guidelines for prostate cancer survivorship care, which reinforce the ACSM guidelines and highlight the benefits of exercise regarding cardiovascular risk management (Skolarus *et al.*, 2014). Irish efforts to progress services may learn from the development of the national Cardiac Rehabilitation model of care. The introduction of a Cardiovascular Health Strategy in 1999 demonstrates how policy can drive development of services. Within 4 years of the introduction of the strategy the number of hospitals providing cardiac rehabilitation increased from 29% to 77% (Lavin *et al.*, 2005). Similar advancements in policy, relating to cancer survivorship care, are needed in the Irish healthcare system. Policy changes encouraged investment in staffing and facilities in all relevant hospitals involved in the delivery of care to patients with cardiovascular disease. This investment is now needed for in cancer rehabilitation

services. Researchers and clinicians alike need to engage with the NCCP, tasked with implementing the new cancer strategy, about the need for services in this area, to ensure the body of knowledge supporting the field of exercise oncology is reflected in clinical practice.

A recent Delphi study completed by oncology healthcare professionals in Ireland identified four themes that could optimise the referral process to community-based exercise programmes for patients with cancer. These included providing education to healthcare professionals and patients regarding the benefits of physical activity. Additional themes focussed on the logistics and quality of programmes, and optimising the logistics of the referral process (Cantwell *et al.*, 2017). The impressive ability of exercise to potentially modulate cancer-specific outcomes is of direct clinical interest. Future research should focus on the implementation of cancer rehabilitation programmes into clinical practice, in order to resolve a disconnect between cancer care and rehabilitation for cancer survivors in Ireland.

7.2.4. Precision Based Medicine in Exercise Oncology

Chapter 6 of this thesis provides greater knowledge in the area of precision based medicine in the area of oncology. This concept has emerged in the last ten years in response to an increasing body of knowledge about the benefits of exercise in oncology, and the fact that the benefits associated with exercise may be particularly relevant for certain groups of patients diagnosed with cancer. The primary goal of precision medicine is to give an intervention to patients who will benefit and avoid providing it to patients who will either not benefit or be harmed. A secondary goal is to avoid the side effects and costs of giving the intervention to patients who will either not benefit or who will be harmed (Friedenreich *et al.*, 2016). This medical model of precision medicine can now be applied in exercise oncology, where certain tumour types or tumour sub-groups will benefit from different exercise interventions. For example, in one large epidemiological analysis, it emerged that among men with biopsy Gleason sum <7 (n = 1034), walking seven or more hours per week was associated with a 61% reduction in risk of prostate cancer progression compared to walking less than half an hour per week (HR: 0.39; 95% CI: 0.11, 1.41). However, no significant reduction was found in risk among men with biopsy Gleason sum ≥7 (n = 421; HR: 1.33; 95% CI: 0.54, 3.29) (Richman *et al.*, 2011). It is apparent that the dosage of exercise prescribed in the ExPeCT trial was not sufficient to result in changes in psycho-social measures, and therefore future studies should

explore alternative outcomes associated with exercise interventions, or alternative doses of exercise. Additionally, future exercise intervention may benefit from the input of many members of the multi-disciplinary team eg. Psycho-oncology services to meet the psychological needs. Rehabilitation is the process of helping a person to reach their fullest potential, including physical potential. Palliative rehabilitation's primary goal is the reduction of dependence in mobility and self-care activities in association with the provision of comfort and emotional support. Therefore, incorporating additional aspects of rehabilitation, such as psycho-oncology services to meet the psychological needs of patients, may be important. Increasing physical activity and engaging in physical activity can be essential components of rehabilitation (Javier and Montagnini, 2011). While small studies have demonstrated the benefits of exercise in palliative populations (Oldervoll, 2011, Porock, 2000), the type of exercise can vary widely, from active-assisted exercise to progressive resistance exercise, or aerobic exercise such as that in the ExPeCT study. Each palliative patient will have different exercise capabilities, and the suitability of exercise as a component of rehabilitation will need to considered carefully. As in other complex populations, any exercise programme should be individualised and based on the patient's overall prognosis, potential to regain function, and desire and motivation to participate in the programme.

While there is a growing body of evidence demonstrating the potential for physical activity to play a meaningful role in optimising morbidity following an advanced cancer diagnosis, the study of exercise interventions like ExPeCT, which involve biological outcomes, is essential to further examine the potential of exercise for particular tumour groups, such as those with advanced metastatic prostate cancer. To date, the field of exercise oncology has focussed on health-related fitness outcomes and patient-reported outcomes, not cancer outcomes. However, for advanced cancer, exercise is emerging as a synergistic medicine (i.e., increasing the potency or effectiveness of concomitantly applied therapies) and targeted medicine (i.e., exerting its own systemic and localized anticancer effects, independent of other therapies) to underpin delays in disease progression and improvements in survival (Hart *et al.*, 2017). The biological analysis completed on the ExPeCT trial will add further knowledge in this area, potentially identifying the particular response of this advanced prostate group to an aerobic exercise intervention. The increasing interest in cancer outcomes by exercise oncology researchers makes the application of precision medicine (i.e., the focus on genetic and molecular subgroups) much more relevant.

7.2.5. Future Research

There are a number of areas relating to exercise and advanced cancer in need of future research. Some of these areas have been highlighted in this thesis. Firstly, it remains unclear if being physically active increases the risk of skeletal-related events in patients with bone metastases secondary to advanced cancer. Medical, radiation and palliative care consultant oncologists and chartered physiotherapists working in oncology in Ireland, cited fracture risk as the primary concern with exercise prescription in this population, despite a recognition of the importance of exercise participation (Chapter 4, 5a, 5b). Although health professionals can be hesitant to offer exercise advice, not all bone metastases are likely to cause fracture, and little is known about the actual association between physical activity levels and fracture rates (Chapter 1). With increasing evidence supporting the role of exercise in metastatic bone disease, there is a need to address exercise-related concerns among health professionals. Clinical scoring systems such as Mirel's classification, are predictive of pathological fracture risk and are widely used clinically. Such scoring algorithms have considerable potential to inform exercise eligibility in this population; however, to date the applicability of such clinical measures for exercise prescription have been inadequately studied. There is a need for a longitudinal study to examine the relationship between habitual physical activity and skeletal related events in patients with metastatic disease over a prolonged period. This information could help to identify a method of improved clinical fracture risk assessment for exercise prescription. I am a collaborator on a recently funded work which will examine this question.

There is also a need to diversify the tumour types involved in oncology research involving exercise. To date, the vast majority of survivorship programmes have been completed in patients with primary breast cancer and programmes have failed to includea wide variety of cancer types. Importantly, survival rates are improving across a number of cancer types and now increasingly patients with cancers traditionally associated with poorer outcomes are surviving with rehabilitation needs. There is a need to expand programmes to patients diagnosed with other tumour types and expand knowledge of outcomes across different tumour sites. Additionally, limited data exist on the durability of exercise interventions in healthy populations, and even less among cancer survivors (Marcus *et al.*, 2000). In non-cancer samples, research suggests that physical activity intervention effects are typically short-lived, and participants return to baseline levels of physical activity post-intervention (Marcus, 2000). Measuring exercise maintenance among cancer survivors is a relatively new area of study and few studies available have

assessed outcomes beyond 6 months of intervention completion. A review of exercise oncology research to identify future areas in need of attention outlined the need for further large-scale studies assessing both self-reported and/or objective measures of exercise exposure with long-term follow-up and adequate event rates in understudied cancer types (Jones and Alfano, 2013).

The mechanisms underpinning the positive effects of exercise, particularly on disease outcome, are closely related to the metabolic syndrome. An additional need in the area of exercise oncology is an exploration of the role of exercise on symptoms of the metabolic syndrome. Metabolic syndrome and its concomitant diseases are a severe health problem world-wide and most likely will gain even more importance in the future since the prevalence of obesity is rising (Jung and Choi, 2014). The metabolic syndrome includes abdominal obesity, hypertension, dyslipidemia and hyperglycemia and is linked to insulin resistance and the development of diabetes mellitus. Studies support the hypothesis that the metabolic syndrome, or its components, might play an important role in the aetiology and progression of certain cancer types and a worse prognosis for some cancers (Braun *et al.*, 2011). Lifestyle factors such as physical activity, affect the risk of developing the metabolic syndrome. The primary treatment goal in individuals with the metabolic syndrome is to reduce the risk for atherosclerotic disease and type 2 diabetes mellitus. Modification of risk factors by lifestyle changes has an important role to play. Exercise training, especially high-intensity, appears to be highly beneficial in preventing the metabolic syndrome relative to any other currently known interventions (Tjonna *et al.*, 2008). Although the metabolic syndrome is a common long-term complication after cancer treatment, information on its prevalence in cancer survivors compared with the general population, and its association with different cancer treatment strategies, is limited. Further studies are needed to increase evidence in this area.

Two studies currently underway have the potential to greatly improve knowledge on the role of exercise in advanced disease. A systematic review is currently underway to examine the study design, participant and activity characteristics, and objective and patient-reported outcomes in patients with advanced cancer (Lowe *et al.*, 2016). This systematic review will provide a comprehensive and rigorous evidence base from which future research directions for physical activity can be proposed. Exercise has the potential to enhance chemotherapeutic and radiotherapeutic effectiveness, interfere with tumour driven dysregulation of angiogenesis and osteogenesis and delay disease progression and extend survival. The ongoing INTERVAL Trial, part of the Movember Global Prostate Cancer, Exercise and Metabolic Health Initiative, will contribute much

knowledge in the area of exercise and metastatic disease (Saad *et al.*, 2016). This initiative will involve a global multi-centre exercise trial for men with advanced cancer looking at overall survival as an endpoint. Additional endpoints will include measures of strength, physical function and physical activity. This trial has the potential to identify the mechanism of action underpinning the relationship between physical activity and the biology of advanced disease.

The development of new and highly effective targeted anti-cancer therapies brings with it new challenges: namely how to mitigate not only short-term transient toxicities, but also the persistent or late side-effects which emerge when patients have to remain on these therapies for extended periods. This thesis has gathered new evidence in a number of areas related to physical activity and advanced cancer. Firstly, evidence regarding the involvement of both patients with advanced cancer and metastatic cancer in exercise programmes has been synthesised. This evidence demonstrates that patients with advanced cancer can safely participate in exercise trials, and highlights the need for future exercise interventions in this population. In addition, the views of patients, clinicians and physiotherapists in Ireland towards exercise in advanced cancer patients has been examined, a much needed addition to the established literature in early stage cancer. It is clear that work is needed to enhance the perceptions of patients and healthcare professionals of activity as being an important part of disease management. While the health belief model identified many barriers to physical activity, additional work is needed on how perceptions of the benefits of physical activity can be maximised and barriers can be overcome. Finally, the randomised controlled trial completed as a part of this thesis has contributed to the increasing body of knowledge regarding the feasibility of exercise for patients with advanced cancer and may encourage future trials in advanced cancer populations to include those with metastatic disease.

7.3. Conclusion

The findings of this thesis add to the accumulating body of evidence surrounding exercise interventions for patients living with metastatic cancer. Results demonstrate a considerable scope for targeted exercise prescription as an adjunct therapy medical treatments for advanced cancer; however, further education of patients and healthcare professionals is needed in order for exercise to be embraced as a part of standard clinical care. This thesis will inform preliminary safety and efficacy trials in patients with metastatic cancer, paving the way for definitive clinical exercise trials with survival endpoints. This will enable researchers to identify which cancer variables are the most

important outcomes, determinants, and moderators for disease progression in patients with advanced cancer.

8. References

Acquadro, C., Berzon, R., Dubois, D., Leidy, N.K., Marquis, P., Revicki, D. & Rothman, M., 2003. Incorporating the Patient's Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. *Value in Health,* 6**,** 522-531.

Adams, R.N., Mosher, C.E., Blair, C.K., Snyder, D.C., Sloane, R. & Demark-Wahnefried, W., 2015. Cancer survivors' uptake and adherence in diet and exercise intervention trials: An integrative data analysis. *Cancer,* 121**,** 77-83.

Adamsen, L., Quist, M., Andersen, C., Moller, T., Herrstedt, J., Kronborg, D., Baadsgaard, M.T., Vistisen, K., Midtgaard, J., Christiansen, B., Stage, M., Kronborg, M.T. & Rorth, M., 2009. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ,* 339**,** b3410.

Adler, R.A., 2011. Management of osteoporosis in men on androgen deprivation therapy. *Maturitas,* 68**,** 143-147.

Ainsworth, B.E., Haskell, W.L., Herrmann, S.D., Meckes, N., Bassett, D.R., Jr., Tudor-Locke, C., Greer, J.L., Vezina, J., Whitt-Glover, M.C. & Leon, A.S., 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc,* 43**,** 1575-81.

Akman, T., Yavuzsen, T., Sevgen, Z., Ellidokuz, H. & Yilmaz, A.U., 2015. Evaluation of sleep disorders in cancer patients based on Pittsburgh Sleep Quality Index. *Eur J Cancer Care (Engl),* 24**,** 553-9.

Albrecht, T.A. & Taylor, A.G., 2012. Physical activity in patients with advanced-stage cancer: a systematic review of the literature. *Clin J Oncol Nurs,* 16**,** 293-300.

Alibhai, S.M., Rahman, S., Warde, P.R., Jewett, M.A., Jaffer, T. & Cheung, A.M., 2006. Prevention and management of osteoporosis in men receiving androgen deprivation therapy: a survey of urologists and radiation oncologists. *Urology,* 68**,** 126-31.

Allott, E.H., Masko, E.M. & Freedland, S.J., 2013. Obesity and prostate cancer: weighing the evidence. *Eur Urol,* 63**,** 800-9.

American Cancer Society, 2016. *Understanding Advanced Cancer, Metastatic Cancer, and Bone Metastasis* [online]. American Cancer Society. Available from: https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html [Accessed 22nd August 2017]

American Cancer Society (Cancer.org). Treatment of Breast Cancer by Stage [ONLINE]. Available at https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage.html. [Accessed 2 October 2017].

Amling, C.L., Riffenburgh, R.H., Sun, L., Moul, J.W., Lance, R.S., Kusuda, L., Sexton, W.J., Soderdahl, D.W., Donahue, T.F., Foley, J.P., Chung, A.K. & Mcleod, D.G., 2004. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol,* 22**,** 439-45.

Amariglio, R.E., Townsend, M.K., Grodstein, F., Sperling, R.A. and Rentz, D.M., 2011. Specific subjective memory complaints in older persons may indicate poor cognitive function. *Journal of the American Geriatrics Society*, *59*(9), pp.1612-1617.

Andersen, B.L., Derubeis, R.J., Berman, B.S., Gruman, J., Champion, V.L., Massie, M.J., Holland, J.C., Partridge, A.H., Bak, K., Somerfield, M.R. & Rowland, J.H., 2014. Screening, Assessment, and Care of Anxiety and Depressive Symptoms

in Adults With Cancer: An American Society of Clinical Oncology Guideline Adaptation. *Journal of Clinical Oncology,* 32**,** 1605-1619.

Angelis, K.D., Rodrigues, B., Zanesco, A., Oliveira, E.M.D., Evangelista, F.D.S.A., Coelho Junior, H.J., Andreia Delbin, M., Chakur Brum, P., Ramires, P.R., Soares, P.P., Wichi, R.B., Amaral, S.L. & Sanches, I.C., 2017. The importance of animal studies in Exercise Science. *Motriz: Revista de Educação Física,* 23.

Auclerc, G., Antoine, E.C., Cajfinger, F., Brunet-Pommeyrol, A., Agazia, C. & Khayat, D., 2000. Management of advanced prostate cancer. *The Oncologist,* 5**,** 36-44.

Badia, W.J.L.a.P., 2005. *Fundamentals of Behavioural Research*: Wadsworth Inc.

Basch, E., Loblaw, D.A., Oliver, T.K., Carducci, M., Chen, R.C., Frame, J.N., Garrels, K., Hotte, S., Kattan, M.W., Raghavan, D., Saad, F., Taplin, M.-E., Walker-Dilks, C., Williams, J., Winquist, E., Bennett, C.L., Wootton, T., Rumble, R.B., Dusetzina, S.B. & Virgo, K.S., 2014. Systemic Therapy in Men With Metastatic Castration-Resistant Prostate Cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline. *Journal of Clinical Oncology,* 32**,** 3436-3448.

Beaton, R., Pagdin-Friesen, W., Robertson, C., Vigar, C., Watson, H. & Harris, S.R., 2009. Effects of exercise intervention on persons with metastatic cancer: a systematic review. *Physiotherapy Canada,* 61**,** 141-153.

Benca, E., Patsch, J.M., Mayr, W., Pahr, D.H. and Windhager, R., 2016. The insufficiencies of risk analysis of impending pathological fractures in patients with femoral metastases: a literature review. *Bone reports*, *5*, pp.51-56.

Bernat, J.K., Wittmann, D.A., Hawley, S.T., Hamstra, D.A., Helfand, A.M., Haggstrom, D.A., Darwish-Yassine, M. & Skolarus, T.A., 2016. Symptom burden and information needs in prostate cancer survivors: A case for tailored long-term survivorship care. *BJU international,* 118**,** 372-378.

Bishop, A., Foster, N.E., Thomas, E. & Hay, E.M., 2008. How does the self-reported clinical management of patients with low back pain relate to the attitudes and beliefs of health care practitioners? A survey of UK general practitioners and physiotherapists. *Pain,* 135**,** 187-95.

Blanchard, C.M., Stein, K.D., Baker, F., Dent, M.F., Denniston, M.M., Courneya, K.S. & Nehl, E., 2004. Association between current lifestyle behaviors and health-related quality of life in breast, colorectal, and prostate cancer survivors. *Psychology & Health,* 19**,** 1-13.

Blessing, J.D. & Forister, J.G., 2012. *Introduction to research and medical literature for health professionals*: Jones & Bartlett Publishers.

Bohannon, R.W., 1986. Test-retest reliability of hand-held dynamometry during a single session of strength assessment. *Physical therapy*, *66*(2), pp.206-209.

Borg, G.A., 1982. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc,* 14**,** 377-81.

Bostwick, D.G., Burke, H.B., Djakiew, D., Euling, S., Ho, S.-M., Landolph, J., Morrison, H., Sonawane, B., Shifflett, T., Waters, D.J. & Timms, B., 2004. Human prostate cancer risk factors. *Cancer,* 101**,** 2371-2490.

Bourke, L., Doll, H., Crank, H., Daley, A., Rosario, D. & Saxton, J.M., 2011. Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. *Cancer Epidemiology Biomarkers and Prevention,* 20**,** 647-657.

Bourke, L., Homer, K.E., Thaha, M.A., Steed, L., Rosario, D.J., Robb, K.A., Saxton, J.M. & Taylor, S.J.C., 2013. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *British Journal Of Cancer,* 110**,** 831.

Bourke, L., Gilbert, S., Hooper, R., Steed, L.A., Joshi, M., Catto, J.W., Saxton, J.M. & Rosario, D.J., 2014. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. *Eur Urol,* 65**,** 865-72.

Bourke, L., Smith, D., Steed, L., Hooper, R., Carter, A., Catto, J., Albertsen, P.C., Tombal, B., Payne, H.A. & Rosario, D.J., 2015. Exercise for Men with Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol*.

Braun, S., Bitton-Worms, K. & Leroith, D., 2011. The Link between the Metabolic Syndrome and Cancer. *International Journal of Biological Sciences,* 7**,** 1003-1015.

Broderick, J.M., Guinan, E., Kennedy, M.J., Hollywood, D., Courneya, K.S., Culos-Reed, S.N., Bennett, K., Dm, O.D. & Hussey, J., 2013. Feasibility and efficacy of a supervised exercise intervention in de-conditioned cancer survivors during the early survivorship phase: the PEACH trial. *J Cancer Surviv,* 7**,** 551-62.

Brown, G.W., 1974. Meaning, measurement, and stress of life events.

Brown, J.K., Byers, T., Doyle, C., Coumeya, K.S., Demark-Wahnefried, W., Kushi, L.H., Mctieman, A., Rock, C.L., Aziz, N., Bloch, A.S., Eldridge, B., Hamilton, K., Katzin, C., Koonce, A., Main, J., Mobley, C., Morra, M.E., Pierce, M.S., Sawyer, K.A. & American Cancer, S., 2003. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin,* 53**,** 268-91.

Brown, J.C., Winters-Stone, K., Lee, A. & Schmitz, K.H., 2012. Cancer, Physical Activity, and Exercise. *Comprehensive Physiology,* 2**,** 2775-2809.

Brown, J.C., Harhay, M.O. & Harhay, M.N., 2015. Physical function as a prognostic biomarker among cancer survivors. *Br J Cancer,* 112**,** 194-8.

Bunting, R., Lamont-Havers, W., Schweon, D. & Kliman, A., 1985. Pathologic fracture risk in rehabilitation of patients with bony metastases. *Clinical Orthopaedics And Related Research***,** 222-227.

Bunting, R.W., Boublik, M., Blevins, F.T., Dame, C.C., Ford, L.A. & Lavine, L.S., 1992. Functional outcome of pathologic fracture secondary to malignant disease in a rehabilitation hospital. *Cancer,* 69**,** 98-102.

Bunting, R.W. & Shea, B., 2001. Bone metastasis and rehabilitation. *Cancer,* 92**,** 1020-8.

Buysse, D.J., Reynolds, C.F., 3rd, Monk, T.H., Berman, S.R. & Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res,* 28**,** 193-213.

Cantwell, M., Walsh, D., Furlong, B., Moyna, N., Mccaffrey, N., Boran, L., Smyth, S. & Woods, C., 2017. Healthcare professionals' knowledge and practice of physical activity promotion in cancer care: Challenges and solutions. *Eur J Cancer Care (Engl)*.

Capanna R, C.L., Coleman R, Et Al. Editors., 2005. *Textbook of Bone Metastases* Hoboken, NJ: John Wiley and Sons.

Carlson, M.D.A. & Morrison, R.S., 2009. Study Design, Precision, and Validity in Observational Studies. *Journal of Palliative Medicine,* 12**,** 77-82.

Carlin, L., Sibley, K., Jenkinson, R., Kontos, P., Mcglasson, R., Kreder, H.J. & Jaglal, S., 2016. Exploring Canadian surgeons' decisions about postoperative weight bearing for their hip fracture patients. *Journal of Evaluation in Clinical Practice***,** n/a-n/a.

Caro, J.J., Ishak, K.J., Huybrechts, K.F., Raggio, G. & Naujoks, C., 2004. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporosis International,* 15**,** 1003-1008.

Carpenter, C. & Suto, M., 2008. *Qualitative research for occupational and physical therapists: A practical guide*: Blackwell Pub.

Carson, J.W., Carson, K.M., Porter, L.S., Keefe, F.J., Shaw, H. & Miller, J.M., 2007. Yoga for women with metastatic breast cancer: results from a pilot study. *J Pain Symptom Manage,* 33**,** 331-41.

Carter, R. & Lubinsky, J., 2015. *Rehabilitation Research-E-Book: Principles and Applications*: Elsevier Health Sciences.

Caspersen, C.J., Powell, K.E. & Christenson, G.M., 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports,* 100**,** 126-131.

Cella, D., Nichol, M.B., Eton, D., Nelson, J.B. & Mulani, P., 2009. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health,* 12**,** 124-9.

Center, M.M., Jemal, A., Lortet-Tieulent, J., Ward, E., Ferlay, J., Brawley, O. & Bray, F., 2012. International variation in prostate cancer incidence and mortality rates. *European urology,* 61**,** 1079-1092.

Chang, S.S., 2007. Treatment Options for Hormone-Refractory Prostate Cancer. *Reviews in Urology,* 9**,** S13-S18.

Chang, B.H., Hendricks, A.M., Slawsky, M.T. & Locastro, J.S., 2004. Patient recruitment to a randomized clinical trial of behavioral therapy for chronic heart failure. *BMC Med Res Methodol,* 4**,** 8.

Charalambous, A. & Kouta, C., 2016. Cancer Related Fatigue and Quality of Life in Patients with Advanced Prostate Cancer Undergoing Chemotherapy. *Biomed Res Int,* 2016**,** 3989286.

Chasan-Taber, S., Rimm, E.B., Stampfer, M.J., Spiegelman, D., Colditz, G.A., Giovannucci, E., Ascherio, A. & Willett, W.C., 1996. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology,* 7**,** 81-6.

Cheville, A.L., Girardi, J., Clark, M.M., Rummans, T.A., Pittelkow, T., Brown, P., Hanson, J., Atherton, P., Johnson, M.E., Sloan, J.A. & Gamble, G., 2010. Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well-being. *Am J Phys Med Rehabil,* 89**,** 611-9.

Chintalacharuvu, S., Wolos, J., Misener, E., Bull, C., Li, L. & Brune, K., 2011. Localized tumor growth in bone: Quantification of tumor burden, bone destruction, and weight bearing. *Journal of Bone and Mineral Research,* 26.

Chiarotto, J.A., Akbarali, R., Bellotti, L. & Dranitsaris, G., 2017. A structured group exercise program for patients with metastatic cancer receiving chemotherapy and CTNNB1 (beta-catenin) as a biomarker of exercise efficacy. *Cancer Manag Res,* 9**,** 495-501.

Chow, E., James, J., Barsevick, A., Hartsell, W., Ratcliffe, S., Scarantino, C., Ivker, R., Roach, M., Suh, J., Petersen, I., Konski, A., Demas, W. & Bruner, D., 2010. Functional interference clusters in cancer patients with bone metastases: a secondary analysis of RTOG 9714. *Int J Radiat Oncol Biol Phys,* 76**,** 1507-11.

Clark, J.A., Wray, N., Brody, B., Ashton, C., Giesler, B. & Watkins, H., 1997. Dimensions of quality of life expressed by men treated for metastatic prostate cancer. *Soc Sci Med,* 45**,** 1299-309.

Coats, V., Maltais, F., Simard, S., Frechette, E., Tremblay, L., Ribeiro, F. & Saey, D., 2013. Feasibility and effectiveness of a home-based exercise training program before lung resection surgery. *Canadian Respiratory Journal,* 20**,** e10-e16.

Cohen, J., 1992. A power primer. *Psychol Bull,* 112**,** 155-9.

Cohen, S., Kamarck, T. & Mermelstein, R., 1983. A global measure of perceived stress. *J Health Soc Behav,* 24**,** 385-96.

Cohen, S.R., Mount, B.M., Strobel, M.G. and Bui, F., 1995. The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. *Palliative medicine*, *9*(3), pp.207-219.

Coleman, R.E., 2005. Bisphosphonates in breast cancer. *Ann Oncol,* 16**,** 687-95.

Coleman, R.E., 2006. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res,* 12**,** 6243s-6249s.

Coleman, S., Berg, C.J. & Thompson, N.J., 2014. Social support, nutrition intake, and physical activity in cancer survivors. *Am J Health Behav,* 38**,** 414-9.
Comet Initiative, 2013. *Core Outcome Measures for Effectiveness Studies* [online]. http://www.comet-initiative.org/ [Accessed 5th March 2016].
Conte, P. & Coleman, R., 2004. Bisphosphonates in the treatment of skeletal metastases. *Semin Oncol,* 31**,** 59-63.
Coons, S.J., Rao, S., Keininger, D.L. & Hays, R.D., 2000. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics,* 17**,** 13-35.
Corbin, J. & Strauss, A., 1990. Grounded theory research: Procedures, canons and evaluative criteria. *Zeitschrift für Soziologie,* 19**,** 418-427.
Cormie, P., Newton, R.U., Spry, N., Joseph, D., Taaffe, D.R. & Galvao, D.A., 2013a. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis,* 16**,** 328-35.
Cormie, P., Newton, R.U., Spry, N., Joseph, D., Taaffe, D.R. & Galvao, D.A., 2013b. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer and Prostatic Diseases,* 16**,** 328-335.
Cormie, P., Galvao, D.A., Spry, N., Joseph, D., Taaffe, D.R. & Newton, R.U., 2014. Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study. *Support Care Cancer,* 22**,** 1537-48.
Cosman, F., De Beur, S., Leboff, M., Lewiecki, E., Tanner, B., Randall, S. & Lindsay, R., 2014. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis international,* 25**,** 2359-2381.
Courneya, K.S., Friedenreich, C.M., Quinney, H.A., Fields, A.L., Jones, L.W. & Fairey, A.S., 2003. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care (Engl),* 12**,** 347-57.
Courneya, K.S., Segal, R.J., Reid, R.D., Jones, L.W., Malone, S.C., Venner, P.M., Parliament, M.B., Scott, C.G., Quinney, H.A. & Wells, G.A., 2004. Three independent factors predicted adherence in a randomized controlled trial of resistance exercise training among prostate cancer survivors. *J Clin Epidemiol,* 57**,** 571-9.
Courneya, K.S., Segal, R.J., Mackey, J.R., Gelmon, K., Reid, R.D., Friedenreich, C.M., Ladha, A.B., Proulx, C., Vallance, J.K., Lane, K., Yasui, Y. & Mckenzie, D.C., 2007. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol,* 25**,** 4396-404.
Courneya, K.S. & Friedenreich, C.M., 2007. Physical activity and cancer control. *Semin Oncol Nurs,* 23**,** 242-52.
Courneya, K.S., Mckenzie, D.C., Reid, R.D., Mackey, J.R., Gelmon, K., Friedenreich, C.M., Ladha, A.B., Proulx, C., Lane, K., Vallance, J.K. & Segal, R.J., 2008. Barriers to supervised exercise training in a randomized controlled trial of breast cancer patients receiving chemotherapy. *Annals of Behavioral Medicine,* 35**,** 116-122.
Craike, M., Gaskin, C.J., Courneya, K.S., Fraser, S.F., Salmon, J., Owen, P.J., Broadbent, S. & Livingston, P.M., 2016. Predictors of adherence to a 12-week exercise program among men treated for prostate cancer: ENGAGE study. *Cancer Med,* 5**,** 787-94.
Creswell, J.W. & Poth, C.N., 2017. *Qualitative inquiry and research design: Choosing among five approaches*: Sage publications.
Culos-Reed, S.N., Robinson, J.W., Lau, H., Stephenson, L., Keats, M., Norris, S., Kline, G. & Faris, P., 2010. Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. *Support Care Cancer,* 18**,** 591-9.
Crowe, S., Cresswell, K., Robertson, A., Huby, G., Avery, A. & Sheikh, A., 2011. The case study approach. *BMC Medical Research Methodology,* 11**,** 100-100.

Dacey, M.L., Kennedy, M.A., Polak, R. & Phillips, E.M., 2014. Physical activity counseling in medical school education: a systematic review. *Medical Education Online,* 19**,** 10.3402/meo.v19.24325.

Daley, A.J., Bowden, S.J., Rea, D.W., Billingham, L. & Carmicheal, A.R., 2008. What advice are oncologists and surgeons in the United Kingdom giving to breast cancer patients about physical activity? *International Journal of Behavioral Nutrition and Physical Activity,* 5.

Damron, T.A., Nazarian, A., Entezari, V., Brown, C., Grant, W., Calderon, N., Zurakowski, D., Terek, R.M., Anderson, M.E., Cheng, E.Y., Aboulafia, A.J., Gebhardt, M.C. & Snyder, B.D., 2016. CT-based Structural Rigidity Analysis Is More Accurate Than Mirels Scoring for Fracture Prediction in Metastatic Femoral Lesions. *Clin Orthop Relat Res,* 474**,** 643-51.

Dahele, M., Skipworth, R.J., Wall, L., Voss, A., Preston, T. & Fearon, K.C., 2007. Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. *J Pain Symptom Manage,* 33**,** 676-85.

Demark-Wahnefried, W., Aziz, N.M., Rowland, J.H. & Pinto, B.M., 2005. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *J Clin Oncol,* 23**,** 5814-30.

Deo, P., Nayak, R. & Rajpura, J., 2013. Women's Attitudes and Health Beliefs toward Osteoporosis Screening in a Community Pharmacy. *J Osteoporos,* 2013**,** 650136.

Department of Health. National Cancer Strategy 2017-2026. *In* D.O. Health (ed.).

Department of Health, 2015. Diagnosis, staging and treatment of patients with prostate cancer. *In* D.O. Health (ed.).

Devers, K.J. & Frankel, R.M., 2000. Study design in qualitative research--2: Sampling and data collection strategies. *Educ Health (Abingdon),* 13**,** 263-71.

Dimeo, F., Schwartz, S., Fietz, T., Wanjura, T., Boning, D. & Thiel, E., 2003. Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. *Support Care Cancer,* 11**,** 623-8.

Dimeo, F.C., Tilmann, M.H., Bertz, H., Kanz, L., Mertelsmann, R. & Keul, J., 1997. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer,* 79**,** 1717-22.

Dittus, K.L., Gramling, R.E. & Ades, P.A., 2017. Exercise interventions for individuals with advanced cancer: A systematic review. *Prev Med,* 104**,** 124-132.

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E.S., Humphreys, J., Lee, K., Miaskowski, C., Puntillo, K., Rankin, S. & Taylor, D., 2001. Advancing the science of symptom management. *J Adv Nurs,* 33**,** 668-76.

Dong, S.T., Butow, P.N., Costa, D.S.J., Lovell, M.R. & Agar, M., 2014. Symptom Clusters in Patients With Advanced Cancer: A Systematic Review of Observational Studies. *Journal of Pain and Symptom Management,* 48**,** 411-450.

Dong, S.T., Costa, D.S., Butow, P.N., Lovell, M.R., Agar, M., Velikova, G., Teckle, P., Tong, A., Tebbutt, N.C., Clarke, S.J. and van der Hoek, K., 2016. Symptom clusters in advanced cancer patients: an empirical comparison of statistical methods and the impact on quality of life. *Journal of pain and symptom management*, *51*(1), pp.88-98.

Donovan, J.L., Rooshenas, L., Jepson, M., Elliott, D., Wade, J., Avery, K., Mills, N., Wilson, C., Paramasivan, S. & Blazeby, J.M., 2016. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials,* 17**,** 283.

Drake, M.T., 2013. Osteoporosis and cancer. *Current Osteoporosis Reports,* 11**,** 163-170.

Droz, J.-P., Albrand, G., Gillessen, S., Hughes, S., Mottet, N., Oudard, S., Payne, H., Puts, M., Zulian, G., Balducci, L. & Aapro, M., 2017. Management of Prostate

Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology. *European Urology,* 72**,** 521-531.
Dudzińska-Griszek, J., Szuster, K. & Szewieczek, J., 2017. Grip strength as a frailty diagnostic component in geriatric inpatients. *Clinical Interventions in Aging,* 12**,** 1151-1157.
Dunn, M.W. & Kazer, M.W., 2011. Prostate Cancer Overview. *Seminars in Oncology Nursing,* 27**,** 241-250.
Edge, S.B. & Compton, C.C., 2010. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol,* 17**,** 1471-4.
Egan K, et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. PLoS One. 2011;6(10):e26125.
Eger, A. & Mikulits, W., 2005. Models of epithelial–mesenchymal transition. *Drug Discovery Today: Disease Models,* 2**,** 57-63.
Ehlers, D.K., Rogers, L.Q., Courneya, K.S., Robbs, R.S. and McAuley, E., 2018. Effects of BEAT Cancer randomized physical activity trial on subjective memory impairments in breast cancer survivors. *Psycho-Oncology*, *27*(2), pp.687-690.
Elfil, M. & Negida, A., 2017. Sampling methods in Clinical Research; an Educational Review. *Emergency,* 5**,** e52.
Ellis, T., Boudreau, J.K., Deangelis, T.R., Brown, L.E., Cavanaugh, J.T., Earhart, G.M., Ford, M.P., Foreman, K.B. & Dibble, L.E., 2013. Barriers to exercise in people with Parkinson disease. *Phys Ther,* 93**,** 628-36.
Elo, S., Kääriäinen, M., Kanste, O., Pölkki, T., Utriainen, K. & Kyngäs, H., 2014. Qualitative Content Analysis. *SAGE Open,* 4**,** 2158244014522633.
Elo, S. & Kyngas, H., 2008. The qualitative content analysis process. *J Adv Nurs,* 62**,** 107-15.
Endicott, J., 1984. Measurement of depression in patients with cancer. *Cancer,* 53**,** 2243-9.
Esper, P., Mo, F., Chodak, G., Sinner, M., Cella, D. & Pienta, K.J., 1997. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology,* 50**,** 920-8.
Ewald, B., Attia, J. & Mcelduff, P., 2014. How many steps are enough? Dose-response curves for pedometer steps and multiple health markers in a community-based sample of older Australians. *J Phys Act Health,* 11**,** 509-18.
Eyigor, S. & Kanyilmaz, S., 2014. Exercise in patients coping with breast cancer: An overview. *World J Clin Oncol,* 5**,** 406-11.
Eyigor, S. and Akdeniz, S., 2014. Is exercise ignored in palliative cancer patients?. *World journal of clinical oncology*, *5*(3), p.554.
Farmer, K.C., 1999. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical therapeutics,* 21**,** 1074-1090.
Farris, M.S., Kopciuk, K.A., Courneya, K.S., Mcgregor, S.E., Wang, Q. & Friedenreich, C.M., 2017. Associations of Postdiagnosis Physical Activity and Change from Prediagnosis Physical Activity with Quality of Life in Prostate Cancer Survivors. *Cancer Epidemiol Biomarkers Prev,* 26**,** 179-187.
Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C. & Parkin, D.M., 2010. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer,* 127**,** 2893-917.
Ferriolli, E., Skipworth, R.J., Hendry, P., Scott, A., Stensteth, J., Dahele, M., Wall, L., Greig, C., Fallon, M., Strasser, F., Preston, T. & Fearon, K.C., 2012. Physical activity monitoring: a responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? *J Pain Symptom Manage,* 43**,** 1025-35.
Fidler, M., 1981. Incidence of fracture through metastases in long bones. *Acta Orthop Scand,* 52**,** 623-7.

Figueroa-Fankhanel, F., 2014. Measurement of Stress. *Psychiatric Clinics of North America,* 37**,** 455-487.

Force, U.P.S.T., 2003. Screening for obesity in adults: recommendations and rationale. *Annals of internal medicine,* 139**,** 930.

Ford, E.S., Mokdad, A.H. & Giles, W.H., 2003. Trends in Waist Circumference among U.S. Adults. *Obesity Research,* 11**,** 1223-1231.

Freedland, S.J. & Aronson, W.J., 2004. Examining the Relationship Between Obesity and Prostate Cancer. *Reviews in Urology,* 6**,** 73-81.

Friedenreich, C.M., Neilson, H.K., Farris, M.S. & Courneya, K.S., 2016. Physical Activity and Cancer Outcomes: A Precision Medicine Approach. *Clin Cancer Res,* 22**,** 4766-4775.

Furlan, A.D., Pennick, V., Bombardier, C., Van Tulder, M. & Editorial Board, C.B.R.G., 2009. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976),* 34**,** 1929-41.

G.A.I.N., 2014. *Guidelines for the Rehabilitation of Patients with Metastatic Spinal Cord Compression (MSCC)*.

Gagnon, M, Dartigues JF, Mazaux JM, et al. Self-reported memory complaints and memory performance in elderly French community residents: Results of the PAQUID Research Program. Neuroepidemiology. 1994;13:145–154

Galvao, D.A., Nosaka, K., Taaffe, D.R., Spry, N., Kristjanson, L.J., Mcguigan, M.R., Suzuki, K., Yamaya, K. & Newton, R.U., 2006. Resistance training and reduction of treatment side effects in prostate cancer patients. *Med Sci Sports Exerc,* 38**,** 2045-52.

Galvao, D.A., Taaffe, D.R., Spry, N. & Newton, R.U., 2007. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis,* 10**,** 340-6.

Galvao, D.A., Taaffe, D.R., Spry, N., Joseph, D., Turner, D. & Newton, R.U., 2009. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation. *Prostate Cancer Prostatic Dis,* 12**,** 198-203.

Galvao, D.A., Taaffe, D.R., Spry, N., Joseph, D. & Newton, R.U., 2010. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol,* 28**,** 340-7.

Galvão, D.A., Taaffe, D.R., Cormie, P., Spry, N., Chambers, S.K., Peddle-Mcintyre, C., Baker, M., Denham, J., Joseph, D., Groom, G. & Newton, R.U., 2011. Efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases: A randomized controlled trial. *BMC Cancer,* 11.

Galvão, D.A., Newton, R.U., Gardiner, R.A., Girgis, A., Lepore, S.J., Stiller, A., Mihalopolous, C., Occhipinti, S. & Chambers, S.K., 2015. Compliance to exercise-oncology guidelines in prostate cancer survivors and associations with psychological distress, unmet supportive care needs, and quality of life. *Psycho-Oncology,* 24**,** 1241-1249.

Galvao, D.A., Taaffe, D.R., Spry, N., Cormie, P., Joseph, D., Chambers, S.K., Chee, R., Peddle-Mcintyre, C., Hart, N.H., Baumann, F.T., Denham, J., Baker, M. & Newton, R.U., 2017. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. *Med Sci Sports Exerc*.

Ganesh, V., Zhang, L., Wan, B.A., Drost, L., Tsao, M., Barnes, E., DeAngelis, C., Chung, H., Diaz, P. and Chow, E., 2018. Symptom clusters using the EORTC QLQ-C15-PAL in palliative radiotherapy. *Annals of palliative medicine*, *7*(2), pp.192-204.

Ganz, P.A., 2011. Assessing the quality and value of quality-of-life measurement in breast cancer clinical trials. *J Natl Cancer Inst,* 103**,** 196-9.

Garber, C.E., Greaney, M.L., Riebe, D., Nigg, C.R., Burbank, P.A. & Clark, P.G., 2010. Physical and mental health-related correlates of physical function in community dwelling older adults: a cross sectional study. *BMC Geriatrics,* 10**,** 6.

Garratt, A., Schmidt, L., Mackintosh, A. & Fitzpatrick, R., 2002. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ,* 324**,** 1417.

Ghosh, A. & Berger, A., 2014. Opioids, adjuvants, and interventional options for pain management of symptomatic metastases. *Ann Palliat Med,* 3**,** 172-91.

Gill, P., Stewart, K., Treasure, E. and Chadwick, B., 2008. Methods of data collection in qualitative research: interviews and focus groups. *British dental journal*, *204*(6), p.291.

Girschik, J., Fritschi, L., Heyworth, J. & Waters, F., 2012. Validation of Self-Reported Sleep Against Actigraphy. *Journal of Epidemiology,* 22**,** 462-468.

Glaser, A.W., Fraser, L.K., Corner, J., Feltbower, R., Morris, E.J., Hartwell, G., Richards, M. & Wagland, R., 2013. Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. *BMJ Open,* 3.

Gokaslan, Z.L., York, J.E., Walsh, G.L., Mccutcheon, I.E., Lang, F.F., Putnam, J.B., Jr., Wildrick, D.M., Swisher, S.G., Abi-Said, D. & Sawaya, R., 1998. Transthoracic vertebrectomy for metastatic spinal tumors. *J Neurosurg,* 89**,** 599-609.

Golden-Kreutz, D.M., Browne, M.W., Frierson, G.M. & Andersen, B.L., 2004. Assessing Stress in Cancer Patients. *Assessment,* 11**,** 216-223.

Goodheart, J.R., Cleary, R.J., Damron, T.A. & Mann, K.A., 2015. Simulating activities of daily living with finite element analysis improves fracture prediction for patients with metastatic femoral lesions. *Journal of Orthopaedic Research,* 33**,** 1226-1234.

Granger, C.L., Parry, S.M., Denehy, L. & Remedios, L., 2018. Evidence, education and multi-disciplinary integration are needed to embed exercise into lung cancer clinical care: A qualitative study involving physiotherapists. *Physiotherapy Theory and Practice***,** 1-9.

Grbich, C., 2012. *Qualitative data analysis: An introduction*: Sage.

Groenvold, M., Petersen, M.A., Aaronson, N.K., Arraras, J.I., Blazeby, J.M., Bottomley, A., Fayers, P.M., de Graeff, A., Hammerlid, E., Kaasa, S. and Sprangers, M.A., 2006. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *European Journal of Cancer*, *42*(1), pp.55-64.

Guest, G., Bunce, A. & Johnson, L., 2006. How Many Interviews Are Enough?:An Experiment with Data Saturation and Variability. *Field Methods,* 18**,** 59-82.

Guinan, E.M., Connolly, E.M., Kennedy, M.J. & Hussey, J., 2013. The presentation of metabolic dysfunction and the relationship with energy output in breast cancer survivors: a cross-sectional study. *Nutr J,* 12**,** 99.

Gwet, K.L., 2014. Intrarater Reliability. *Wiley StatsRef: Statistics Reference Online.* John Wiley & Sons, Ltd.

Hart, N.H., Galvão, D.A. & Newton, R.U., 2017a. Exercise medicine for advanced prostate cancer. *Current Opinion in Supportive and Palliative Care,* 11**,** 247-257.

Hart, N.H., Newton, R.U., Spry, N.A., Taaffe, D.R., Chambers, S.K., Feeney, K.T., Joseph, D.J., Redfern, A.D., Ferguson, T. & Galvao, D.A., 2017. Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy. *BMJ Open,* 7**,** e014458.

Hayden, J.A., Van Tulder, M.W. & Tomlinson, G., 2005. Systematic review: strategies for using exercise therapy to improve outcomes in chronic low back pain. *Ann Intern Med,* 142**,** 776-85.

Hayes, 2016. *Patient education: Treatment of metastatic breast cancer (Beyond the Basics)* [online]. https://www.uptodate.com/contents/treatment-of-metastatic-breast-cancer-beyond-the-basics [Accessed April 22nd 2017].

Hayes, S.C., Spence, R.R., Galvao, D.A. & Newton, R.U., 2009. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport,* 12**,** 428-34.

Headley, J.A., Ownby, K.K. & John, L.D., 2004. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. *Oncology nursing forum,* 31**,** 977-983.

Hefferon, K., Murphy, H., Mcleod, J., Mutrie, N. & Campbell, A., 2013. Understanding barriers to exercise implementation 5-year post-breast cancer diagnosis: a large-scale qualitative study. *Health Educ Res,* 28**,** 843-56.

Heim, H.M. & Oei, T.P., 1993. Comparison of prostate cancer patients with and without pain. *Pain,* 53**,** 159-162.

Hinz, A., Mehnert, A., Kocalevent, R.D., Brahler, E., Forkmann, T., Singer, S. & Schulte, T., 2016. Assessment of depression severity with the PHQ-9 in cancer patients and in the general population. *BMC Psychiatry,* 16**,** 22.

Holden, M.A., Haywood, K.L., Potia, T.A., Gee, M. & Mclean, S., 2014. Recommendations for exercise adherence measures in musculoskeletal settings: a systematic review and consensus meeting (protocol). *Syst Rev,* 3**,** 10.

Holmes, M.D., Chen, W.Y., Feskanich, D., Kroenke, C.H. & Colditz, G.A., 2005. Physical activity and survival after breast cancer diagnosis. *JAMA,* 293**,** 2479-86.

Hortobagyi, G.N., 2011. Commentary: Role of Bone-Modifying Agents in Metastatic Breast Cancer. *Journal of Oncology Practice,* 7**,** 121-123.

Hovsepian, K., Al'absi, M., Ertin, E., Kamarck, T., Nakajima, M. & Kumar, S., 2015. Stress: Towards a Gold Standard for Continuous Stress Assessment in the Mobile Environment. *Proceedings of the ... ACM International Conference on Ubiquitous Computing . UbiComp (Conference),* 2015**,** 493-504.

Howick, Glasziou, T. Greenhalgh, C. Heneghan, A. Liberati, I. Moschetti, B. Phillips, and H. Thornton. , "Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)".

Hsieh, H.F. & Shannon, S.E., 2005. Three approaches to qualitative content analysis. *Qual Health Res,* 15**,** 1277-88.

Hlubocky, F.J., Sher, T., Cella, D., Yap, B.J., Ratain, M.J., Peppercorn, J. and Daugherty, C., 2017. The impact of sleep disturbances (SD) on quality of life, psychological morbidity, and survival of advanced cancer patients (ACP) and caregivers (CG).

Humphrey, P.A., 2004. Gleason grading and prognostic factors in carcinoma of the prostate. *Mod Pathol,* 17**,** 292-306.

Hussain, S.A., Weston, R., Stephenson, R.N., George, E. & Parr, N.J., 2003. Immediate dual energy X-ray absorptiometry reveals a high incidence of osteoporosis in patients with advanced prostate cancer before hormonal manipulation. *BJU International,* 92**,** 690-694.

Hwang, C.L., Yu, C.J., Shih, J.Y., Yang, P.C. & Wu, Y.T., 2012. Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. *Supportive Care in Cancer,* 20**,** 3169-3177.

Hwang, J.H., Chang, H.J., Shim, Y.H., Park, W.H., Park, W., Huh, S.J. & Yang, J.H., 2008. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. *Yonsei Med J,* 49**,** 443-50.

Institute, N.C., 2017. *What is cancer?* [online]. National Cancer Institute Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer [Accessed 5th January 2016]

Irwin, M.L., Crumley, D., Mctiernan, A., Bernstein, L., Baumgartner, R., Gilliland, F.D., Kriska, A. & Ballard-Barbash, R., 2003. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer,* 97**,** 1746-57.

Irwin, M.L., Cadmus, L., Alvarez-Reeves, M., O'neil, M., Mierzejewski, E., Latka, R., Yu, H., Dipietro, L., Jones, B., Knobf, M.T., Chung, G.G. & Mayne, S.T., 2008. Recruiting and retaining breast cancer survivors into a randomized controlled exercise trial: The Yale Exercise and Survivorship Study. *Cancer,* 112**,** 2593-2606.

Ivers, M.E.D., Barbara A.; Bates, Ursula, 2009. *Development, implementation and evaluation of a multidisciplinary cancer rehabilitation programme : The CANSURVIVOR Project : meeting post-treatment cancer survivors' needs*: H.S. Executive.

Jack, K., Mclean, S.M., Moffett, J.K. & Gardiner, E., 2010. Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Man Ther,* 15**,** 220-8.

Jacobs, B.L., Zhang, Y., Skolarus, T.A., Wei, J.T., Montie, J.E., Miller, D.C. & Hollenbeck, B.K., 2014. Comparative Effectiveness of External-Beam Radiation Approaches for Prostate Cancer. *European Urology,* 65**,** 162-168.

Jani, A.B., 2006. Management strategies for locally advanced prostate cancer. *Drugs Aging,* 23**,** 119-29.

Janssen, S.J., Paulino Pereira, N.R., Raskin, K.A., Ferrone, M.L., Hornicek, F.J., Van Dijk, C.N., Lozano-Calderon, S.A. & Schwab, J.H., 2016. A comparison of questionnaires for assessing physical function in patients with lower extremity bone metastases. *J Surg Oncol,* 114**,** 691-696.

Janz, N.K. & Becker, M.H., 1984. The Health Belief Model: a decade later. *Health Educ Q,* 11**,** 1-47.

Javier, N.S. and Montagnini, M.L., 2011. Rehabilitation of the hospice and palliative care patient. *Journal of palliative medicine*, *14*(5), pp.638-648.

Jawad, M.U. & Scully, S.P., 2010. In brief: classifications in brief: Mirels' classification: metastatic disease in long bones and impending pathologic fracture. *Clin Orthop Relat Res,* 468**,** 2825-7.

Jenney, M.E. & Campbell, S., 1997. Measuring quality of life. *Arch Dis Child,* 77**,** 347-50.

Jensen, W., Baumann, F.T., Stein, A., Bloch, W., Bokemeyer, C., De Wit, M. & Oechsle, K., 2014. Exercise training in patients with advanced gastrointestinal cancer undergoing palliative chemotherapy: A pilot study. *Supportive Care in Cancer,* 22**,** 1797-1806.

Jensen, R.E., Potosky, A.L., Reeve, B.B., Hahn, E., Cella, D., Fries, J., Smith, A.W., Keegan, T.H., Wu, X.C., Paddock, L. & Moinpour, C.M., 2015. Validation of the PROMIS physical function measures in a diverse US population-based cohort of cancer patients. *Qual Life Res,* 24**,** 2333-44.

Jin, J., Sklar, G.E., Min Sen Oh, V. & Chuen Li, S., 2008. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag,* 4**,** 269-86.

Jones, C.J., Rikli, R.E. & Beam, W.C., 1999. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport,* 70**,** 113-9.

Jones, L.W. & Courneya, K.S., 2002. Exercise discussions during cancer treatment consultations. *Cancer Pract,* 10**,** 66-74.

Jones, L.W., Courneya, K.S., Fairey, A.S. & Mackey, J.R., 2004. Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial. *Ann Behav Med,* 28**,** 105-13.

Jones, L.W., Courneya, K.S., Peddle, C. & Mackey, J.R., 2005. Oncologists' opinions towards recommending exercise to patients with cancer: a Canadian national survey. *Support Care Cancer,* 13**,** 929-37.

Jones, L.W., Guill, B., Keir, S.T., Carter, K., Friedman, H.S., Bigner, D.D. & Reardon, D.A., 2007. Exercise interest and preferences among patients diagnosed with primary brain cancer. *Support Care Cancer,* 15**,** 47-55.

Jones, L.W., Eves, N.D. & Peppercorn, J., 2010. Pre-exercise screening and prescription guidelines for cancer patients. *Lancet Oncol,* 11**,** 914-6.

Jones, L.W. & Alfano, C.M., 2013. Exercise-oncology research: past, present, and future. *Acta Oncol,* 52**,** 195-215.

Jones, L.W., Antonelli, J., Masko, E.M., Broadwater, G., Lascola, C.D., Fels, D., Dewhirst, M.W., Dyck, J.R., Nagendran, J., Flores, C.T., Betof, A.S., Nelson, E.R., Pollak, M., Dash, R.C., Young, M.E. & Freedland, S.J., 2012a. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985),* 113**,** 263-72.

Jones, L.W., Hornsby, W.E., Goetzinger, A., Forbes, L.M., Sherrard, E.L., Quist, M., Lane, A.T., West, M., Eves, N.D., Gradison, M., Coan, A., Herndon, J.E. & Abernethy, A.P., 2012b. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer,* 76**,** 248-52.

Jung, U.J. & Choi, M.S., 2014. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci,* 15**,** 6184-223.

Jw, C., 2012. *Educational Research: Planning, Conducting, and Evaluating Quantitative and Qualitative Research,* 4th Edition ed. Boston MA: Pearson Education.

Kadam, P. & Bhalerao, S., 2010. Sample size calculation. *International Journal of Ayurveda Research,* 1**,** 55-57.

Kadam, R.A., Borde, S.U., Madas, S.A., Salvi, S.S. & Limaye, S.S., 2016. Challenges in recruitment and retention of clinical trial subjects. *Perspectives in Clinical Research,* 7**,** 137-143.

Kanis, J.A., Delmas, P., Burckhardt, P., Cooper, C. & Torgerson, D., 1997. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int,* 7**,** 390-406.

Karanicolas, P.J., Farrokhyar, F. & Bhandari, M., 2010. Blinding: Who, what, when, why, how? *Canadian Journal of Surgery,* 53**,** 345-348.

Karvinen, K.H., Courneya, K.S., Campbell, K.L., Pearcey, R.G., Dundas, G., Capstick, V. & Tonkin, K.S., 2006. Exercise preferences of endometrial cancer survivors: a population-based study. *Cancer Nurs,* 29**,** 259-65.

Kenfield, S.A., Stampfer, M.J., Giovannucci, E. & Chan, J.M., 2011. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol,* 29**,** 726-32.Keogh, J.W., Olsen, A., Climstein, M., Sargeant, S. & Jones, L., 2015. Benefits and Barriers of Cancer Practitioners Discussing Physical Activity with their Cancer Patients. *J Cancer Educ*.

Kernan, W.N., Viscoli, C.M., Makuch, R.W., Brass, L.M. and Horwitz, R.I., 1999. Stratified randomization for clinical trials. *Journal of clinical epidemiology*, *52*(1), pp.19-26.

Kinser, P.A. and Robins, J.L., 2013. Control group design: enhancing rigor in research of mind-body therapies for depression. *Evidence-Based Complementary and Alternative Medicine*, *2013*.

Kirby, A., Gebski, V. & Keech, A.C., 2002. Determining the sample size in a clinical trial. *Med J Aust,* 177**,** 256-7.

Klassen, O., Schmidt, M.E., Ulrich, C.M., Schneeweiss, A., Potthoff, K., Steindorf, K. & Wiskemann, J., 2017. Muscle strength in breast cancer patients receiving different treatment regimes. *J Cachexia Sarcopenia Muscle,* 8**,** 305-316.

Klein, J., 2002. Issues surrounding the use of the Internet for data collection. *American Journal of Occupational Therapy,* 56**,** 340-343.

Knols, R., Aaronson, N.K., Uebelhart, D., Fransen, J. & Aufdemkampe, G., 2005. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *J Clin Oncol,* 23**,** 3830-42.

Kohl, H.W., Gibbons, L.W., Gordon, N.F. & Blair, S.N., 1990. An empirical evaluation of the ACSM guidelines for exercise testing. *Med Sci Sports Exerc,* 22**,** 533-9.

Kohrt, W.M., Bloomfield, S.A., Little, K.D., Nelson, M.E., Yingling, V.R. & American College of Sports, M., 2004. American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc,* 36**,** 1985-96.

Koizumi, D., Rogers, N.L., Rogers, M.E., Islam, M.M., Kusunoki, M. & Takeshima, N., 2009. Efficacy of an accelerometer-guided physical activity intervention in community-dwelling older women. *J Phys Act Health,* 6**,** 467-74

Kroenke, K., Spitzer, R.L. & Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med,* 16**,** 606-13.

Kuehr, L., Wiskemann, J., Abel, U., Ulrich, C.M., Hummler, S. & Thomas, M., 2014. Exercise in Patients with Non-Small Cell Lung Cancer. *Medicine & Science in Sports & Exercise,* 46**,** 656-663.

Laird, B.J., Walley, J., Murray, G.D., Clausen, E., Colvin, L.A. & Fallon, M.T., 2011. Characterization of cancer-induced bone pain: an exploratory study. *Support Care Cancer,* 19**,** 1393-401.

Laird, B.J., Scott, A.C., Colvin, L.A., Mckeon, A.L., Murray, G.D., Fearon, K.C. & Fallon, M.T., 2011. Pain, depression, and fatigue as a symptom cluster in advanced cancer. *J Pain Symptom Manage,* 42**,** 1-11.

Latham, N.K., Mehta, V., Nguyen, A.M., Jette, A.M., Olarsch, S., Papanicolaou, D. & Chandler, J., 2008. Performance-based or self-report measures of physical function: which should be used in clinical trials of hip fracture patients? *Arch Phys Med Rehabil,* 89**,** 2146-55.

Lauderdale, D.S., Knutson, K.L., Yan, L.L., Liu, K. & Rathouz, P.J., 2008. Sleep duration: how well do self-reports reflect objective measures? The CARDIA Sleep Study. *Epidemiology (Cambridge, Mass.),* 19**,** 838-845.

Lavin, D., Hevey, D., Mcgee, H.M., De La Harpe, D., Kiernan, M. & Shelley, E., 2005. Cardiac rehabilitation services in Ireland: the impact of a coordinated national development strategy. *Irish Journal of Medical Science,* 174**,** 33-38.

Law, M.R., Morris, J.K. & Wald, N.J., 2009. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ,* 338**,** b1665.

Layne, T.M., Graubard, B.I., Ma, X., Mayne, S.T. and Albanes, D., 2018. Prostate cancer risk factors in black and white men in the NIH-AARP Diet and Health Study. *Prostate cancer and prostatic diseases*, p.1.

Lee, R.J., Saylor, P.J. & Smith, M.R., 2011. Treatment and prevention of bone complications from prostate cancer. *Bone,* 48**,** 88-95.

Levine, G.N., D'amico, A.V., Berger, P., Clark, P.E., Eckel, R.H., Keating, N.L., Milani, R.V., Sagalowsky, A.I., Smith, M.R., Zakai, N., American Heart Association Council on Clinical, C., Council On, E., Prevention, T.a.C.S. & The American Urological, A., 2010. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *CA Cancer J Clin,* 60**,** 194-201.

Levinger, I., Bronks, R., Cody, D.V., Linton, I. & Davie, A., 2004. Perceived Exertion As an Exercise Intensity Indicator in Chronic Heart Failure Patients on Beta-Blockers. *Journal of Sports Science & Medicine,* 3**,** 23-27.

Li, T., Wei, S., Shi, Y., Pang, S., Qin, Q., Yin, J., Deng, Y., Chen, Q., Wei, S., Nie, S. & Liu, L., 2015. The dose-response effect of physical activity on cancer mortality: findings from 71 prospective cohort studies. *Br J Sports Med*.

Ligibel, J.A., Giobbie-Hurder, A., Shockro, L., Campbell, N., Partridge, A.H., Tolaney, S.M., Lin, N.U. & Winer, E.P., 2016. Randomized trial of a physical activity intervention in women with metastatic breast cancer. *Cancer,* 122**,** 1169-77.

Lindqvist, O., Widmark, A. & Rasmussen, B.H., 2006. Reclaiming Wellness-Living With Bodily Problems, As Narrated by Men With Advanced Prostate Cancer. *Cancer Nursing,* 29**,** 327-337.

Lipton, A., Uzzo, R., Amato, R.J., Ellis, G.K., Hakimian, B., Roodman, G.D. & Smith, M.R., 2009. The science and practice of bone health in oncology: managing bone loss and metastasis in patients with solid tumors. *J Natl Compr Canc Netw,* 7 Suppl 7**,** S1-29; quiz S30.

Litterini, A.J., Fieler, V.K., Cavanaugh, J.T. & Lee, J.Q., 2013. Differential effects of cardiovascular and resistance exercise on functional mobility in individuals with advanced cancer: a randomized trial. *Arch Phys Med Rehabil,* 94**,** 2329-35.

Loblaw, D.A., Virgo, K.S., Nam, R., Somerfield, M.R., Ben-Josef, E., Mendelson, D.S., Middleton, R., Sharp, S.A., Smith, T.J., Talcott, J., Taplin, M., Vogelzang, N.J., Wade, J.L., 3rd, Bennett, C.L. & Scher, H.I., 2007. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol,* 25**,** 1596-605.

Lowe, S.S., Watanabe, S.M., Baracos, V.E. & Courneya, K.S., 2009. Associations Between Physical Activity and Quality of Life in Cancer Patients Receiving Palliative Care: A Pilot Survey. *Journal of Pain and Symptom Management,* 38**,** 785-796.

Lowe, S.S., Watanabe, S.M., Baracos, V.E. & Courneya, K.S., 2010. Physical activity interests and preferences in palliative cancer patients. *Supportive Care in Cancer,* 18**,** 1469-1475.

Lowe, S.S., Watanabe, S.M., Baracos, V.E. & Courneya, K.S., 2013. Home-based functional walking program for advanced cancer patients receiving palliative care: A case series. *BMC Palliative Care,* 12.

Lowe, S.S., Tan, M., Faily, J., Watanabe, S.M. & Courneya, K.S., 2016. Physical activity in advanced cancer patients: a systematic review protocol. *Systematic Reviews,* 5**,** 43

Lowe, S.S., Danielson, B., Beaumont, C., Watanabe, S.M. & Courneya, K.S., 2016. Physical activity interests and preferences of cancer patients with brain metastases: a cross-sectional survey. *BMC Palliat Care,* 15**,** 7.

Luborsky, M.R. & Rubinstein, R.L., 1995. Sampling in Qualitative Research: Rationale, Issues, and Methods. *Research on aging,* 17**,** 89-113.

Lutz, S., Lo, S.S., Chow, E., Sahgal, A. & Hoskin, P., 2010. Radiotherapy for metastatic bone disease: Current standards and future prospectus. *Expert Review of Anticancer Therapy,* 10**,** 683-695.

Lynch, B.M., 2010. Sedentary behavior and cancer: a systematic review of the literature and proposed biological mechanisms. *Cancer Epidemiol Biomarkers Prev,* 19**,** 2691-709.

Lynch, M.E., Brooks, D., Mohanan, S., Lee, M.J., Polamraju, P., Dent, K., Bonassar, L.J., Van Der Meulen, M.C. & Fischbach, C., 2013. In vivo tibial compression decreases osteolysis and tumor formation in a human metastatic breast cancer model. *J Bone Miner Res,* 28**,** 2357-67.

Macefield, R.C., Boulind, C.E. & Blazeby, J.M., 2014. Selecting and measuring optimal outcomes for randomised controlled trials in surgery. *Langenbeck's Archives of Surgery,* 399**,** 263-272.

Macmillan.org.uk. (2019). [online] Available at: https://www.macmillan.org.uk/_images/physical-activity-for-people-with-metastatic-bone-disease-guidance_tcm9-326004.pdf [Accessed 21 Jan. 2019].

Maddocks, M., Mockett, S. & Wilcock, A., 2009. Is exercise an acceptable and practical therapy for people with or cured of cancer? A systematic review. *Cancer Treat Rev,* 35**,** 383-90.

Manzar, M.D., Moiz, J.A., Zannat, W., Spence, D.W., Pandi-Perumal, S.R., Ahmed, S.B. & Hussain, M.E., 2015. Validity of the Pittsburgh Sleep Quality Index in Indian University Students. *Oman Medical Journal,* 30**,** 193-202.

Marcus, B.H., Dubbert, P.M., Forsyth, L.H., Mckenzie, T.L., Stone, E.J., Dunn, A.L. & Blair, S.N., 2000. Physical activity behavior change: issues in adoption and maintenance. *Health Psychol,* 19**,** 32-41.

Martin, S.B., Morrow, J.R., Jr., Jackson, A.W. & Dunn, A.L., 2000. Variables related to meeting the CDC/ACSM physical activity guidelines. *Med Sci Sports Exerc,* 32**,** 2087-92.

Martin, L.R., Williams, S.L., Haskard, K.B. & Dimatteo, M.R., 2005. The challenge of patient adherence. *Ther Clin Risk Manag,* 1**,** 189-99.

Mason, C. and Katzmarzyk, P.T., 2009. Variability in waist circumference measurements according to anatomic measurement site. *Obesity*, *17*(9), pp.1789-1795.

Massy-Westropp, N.M., Gill, T.K., Taylor, A.W., Bohannon, R.W. & Hill, C.L., 2011. Hand Grip Strength: age and gender stratified normative data in a population-based study. *BMC Res Notes,* 4**,** 127.

Mcclain, J.J., Sisson, S.B. & Tudor-Locke, C., 2007. Actigraph accelerometer interinstrument reliability during free-living in adults. *Medicine and science in sports and exercise,* 39**,** 1509-1514.

Mcnamara, M., Sweeney, C., Antonarakis, E.S. & Armstrong, A.J., 2017. The evolving landscape of metastatic hormone-sensitive prostate cancer: a critical review of the evidence for adding docetaxel or abiraterone to androgen deprivation. *Prostate Cancer and Prostatic Diseases*.

Mc Daid, C., Hodges, Z., Fayter, D., Stirk, L. & Eastwood, A., 2006. Increasing participation of cancer patients in randomised controlled trials: a systematic review. *Trials,* 7**,** 16.

Mcdowell, I., 2006. *Measuring health: a guide to rating scales and questionnaires*: Oxford university press.

Mcdowell, I. & Newell, C., 1996. A guide to rating scales and questionnaires. *A guide to rating scales and questionnaires*.

Meyerhardt, J.A., Giovannucci, E.L., Holmes, M.D., Chan, A.T., Chan, J.A., Colditz, G.A. & Fuchs, C.S., 2006. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol,* 24**,** 3527-34.

Miles, J. & Gilbert, P., 2005. *A handbook of research methods for clinical and health psychology*: Oxford University Press on Demand.

Miller, R.D. & Walsh, T.D., 1991. Psychosocial aspects of palliative care in advanced cancer. *Journal of Pain and Symptom Management,* 6**,** 24-29.

Millor, N., Lecumberri, P., Gomez, M., Martinez-Ramirez, A. & Izquierdo, M., 2013. An evaluation of the 30-s chair stand test in older adults: frailty detection based on kinematic parameters from a single inertial unit. *J Neuroeng Rehabil,* 10**,** 86.

Mirels, 1989. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res,* 249.

Mirrakhimov, A.E., 2015. Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. *N Am J Med Sci,* 7**,** 483-93.

Mitchell, K., Graff, M., Hedt, C. & Simmons, J., 2016. Reliability and validity of a smartphone pulse rate application for the assessment of resting and elevated pulse rate. *Physiotherapy Theory and Practice,* 32**,** 494-499.

Mock, V., Dow, K.H., Meares, C.J., Grimm, P.M., Dienemann, J.A., Haisfield-Wolfe, M.E., Quitasol, W., Mitchell, S., Chakravarthy, A. & Gage, I., 1997. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum,* 24**,** 991-1000.

Moher, D., Schulz, K.F., Altman, D.G. & Group, C., 2001. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Elsevier.

Mohler, J., Bahnson, R.R., Boston, B., Busby, J.E., D'amico, A., Eastham, J.A., Enke, C.A., George, D., Horwitz, E.M., Huben, R.P., Kantoff, P., Kawachi, M., Kuettel, M., Lange, P.H., Macvicar, G., Plimack, E.R., Pow-Sang, J.M., Roach, M., 3rd, Rohren, E., Roth, B.J., Shrieve, D.C., Smith, M.R., Srinivas, S., Twardowski, P. & Walsh, P.C., 2010. NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw,* 8**,** 162-200.

Montazeri, A., 2009. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health and Quality of Life Outcomes,* 7**,** 102-102.

Moore, S.C., Peters, T.M., Ahn, J., Park, Y., Schatzkin, A., Albanes, D., Hollenbeck, A. & Leitzmann, M.F., 2009. Age-specific Physical Activity and Prostate Cancer Risk Among White Men and Black Men. *Cancer,* 115**,** 5060-5070.

Morris, Z.S., Wooding, S. and Grant, J., 2011. The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of the Royal Society of Medicine*, *104*(12), pp.510-520.

Moyad, M.A., Newton, R.U., Tunn, U.W. & Gruca, D., 2016. Integrating diet and exercise into care of prostate cancer patients on androgen deprivation therapy. *Res Rep Urol,* 8**,** 133-43.

Murad, M.H., Asi, N., Alsawas, M. and Alahdab, F., 2016. New evidence pyramid. *BMJ Evidence-Based Medicine*, pp.ebmed-2016.

NCCC, 2008. *Metastatic Spinal Cord Compression: Diagnosis and Management of Patients at Risk of or with Metastatic Spinal Cord Compression. ,* (NICE Clinical Guidelines, No. 75.) 6 ed. Cardiff (UK): National Collaborating Centre for Cancer (UK).

NCI, 2017. *NCI Dictionary of Cancer Terms* [online]. National Cancer Institute. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=286105 [Accessed November 10th 2017]

NICE, 2008. Metastatic spinal cord compression in adults: risk assessment, diagnosis and management CG75.

National Cancer Registry, 2017. *Cancer in Ireland 1994-2015 with estimates for 2015-2017.* Cork, Ireland.

Ng, J.Y., Ntoumanis, N., Thogersen-Ntoumani, C., Deci, E.L., Ryan, R.M., Duda, J.L. & Williams, G.C., 2012. Self-Determination Theory Applied to Health Contexts: A Meta-Analysis. *Perspect Psychol Sci,* 7**,** 325-40.

Nadler, M., Bainbridge, D., Tomasone, J., Cheifetz, O., Juergens, R.A. & Sussman, J., 2017. Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. *Supportive Care in Cancer,* 25**,** 2297-2304.

Narayanan, P., 2013. Denosumab: A comprehensive review. *South Asian J Cancer,* 2**,** 272-7.

Oefelein, M.G., Agarwal, P.K. & Resnick, M.I., 2004. Survival of patients with hormone refractory prostate cancer in the prostate specific antigen era. *J Urol,* 171**,** 1525-8.

Okamura, H., 2011. Importance of rehabilitation in cancer treatment and palliative medicine. *Jpn J Clin Oncol,* 41**,** 733-8.

Oldervoll, L.M., Loge, J.H., Paltiel, H., Asp, M.B., Vidvei, U., Hjermstad, M.J. & Kaasa, S., 2005a. Are palliative cancer patients willing and able to participate in a physical exercise program? *Palliative & Supportive Care,* 3**,** 281-287.

Oldervoll, L.M., Loge, J.H., Paltiel, H., Asp, M.B., Vidvei, U., Wiken, A.N., Hjermstad, M.J. & Kaasa, S., 2006. The effect of a physical exercise program in palliative care: A Phase II study. *Journal of Pain and Symptom Management,* 31**,** 421-430.

Oldervoll, L.M., Loge, J.H., Lydersen, S., Paltiel, H., Asp, M.B., Nygaard, U.V., Oredalen, E., Frantzen, T.L., Lesteberg, I., Amundsen, L., Hjermstad, M.J., Haugen, D.F., Paulsen, O. & Kaasa, S., 2011. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncologist,* 16**,** 1649-57

Orji, R., Vassileva, J. & Mandryk, R., 2012. Towards an effective health interventions design: an extension of the health belief model. *Online J Public Health Inform,* 4.

Osanto, S. & Van Poppel, H., 2012. Emerging novel therapies for advanced prostate cancer. *Therapeutic Advances in Urology,* 4**,** 3-12.

Palinkas, L.A., Horwitz, S.M., Green, C.A., Wisdom, J.P., Duan, N. & Hoagwood, K., 2015. Purposeful sampling for qualitative data collection and analysis in mixed method implementation research. *Administration and policy in mental health,* 42**,** 533-544.

Palumbo, M.O., Kavan, P., Miller, W.H., Panasci, L., Assouline, S., Johnson, N., Cohen, V., Patenaude, F., Pollak, M., Jagoe, R.T. & Batist, G., 2013. Systemic cancer therapy: achievements and challenges that lie ahead. *Frontiers in Pharmacology,* 4**,** 57.

Park, J.-H., Oh, M., Yoon, Y.J., Lee, C.W., Jones, L.W., Kim, S.I., Kim, N.K. & Jeon, J.Y., 2015. Characteristics of attitude and recommendation of oncologists toward exercise in South Korea: a cross sectional survey study. *BMC Cancer,* 15**,** 249.

Peeters, C., Stewart, A., Segal, R., Wouterloot, E., Scott, C.G. & Aubry, T., 2009. Evaluation of a cancer exercise program: patient and physician beliefs. *Psychooncology,* 18**,** 898-902.

Penny, S.B., Kathleen, Y., John, C., Kimberly, W. & David, C., 2005. General Population and Cancer Patient Norms for the Functional Assessment of Cancer Therapy-General (FACT-G). *Evaluation & the Health Professions,* 28**,** 192-211.

Penttinen, H., Nikander, R., Blomqvist, C., Luoto, R. & Saarto, T., 2009. Recruitment of breast cancer survivors into a 12-month supervised exercise intervention is feasible. *Contemporary clinical trials,* 30**,** 457-463.

Perry, C.M. & Figgitt, D.P., 2004. Zoledronic acid: a review of its use in patients with advanced cancer. *Drugs,* 64**,** 1197-1211.

Petcu, E.B., Schug, S.A. & Smith, H., 2002. Clinical evaluation of onset of analgesia using intravenous pamidronate in metastatic bone pain. *J Pain Symptom Manage,* 24**,** 281-4.

Pilepich, M.V., Winter, K., John, M.J., Mesic, J.B., Sause, W., Rubin, P., Lawton, C., Machtay, M. & Grignon, D., 2001. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys,* 50**,** 1243-52.

Porock, D., Kristjanson, L.J., Tinnelly, K., Duke, T. & Blight, J., 2000. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care,* 16**,** 30-6.

Prado, C.M., Baracos, V.E., Mccargar, L.J., Reiman, T., Mourtzakis, M., Tonkin, K., Mackey, J.R., Koski, S., Pituskin, E. & Sawyer, M.B., 2009. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res,* 15**,** 2920-6.

Qian, Z., Sun, Z., Yang, H., Gu, Y., Chen, K. & Wu, G., 2011. Kyphoplasty for the treatment of malignant vertebral compression fractures caused by metastases. *Journal of Clinical Neuroscience,* 18**,** 763-767.

Quist, M., Rorth, M., Langer, S., Jones, L.W., Laursen, J.H., Pappot, H., Christensen, K.B. & Adamsen, L., 2012. Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: a pilot study. *Lung Cancer,* 75**,** 203-8.

Quist, M., 2013. Effects of an exercise intervention in early palliative phase for advanced lung cancer patients. *European Journal of Cancer,* 49**,** S377-S378.

Quist, M., Adamsen, L., Rorth, M., Laursen, J.H., Christensen, K.B. & Langer, S.W., 2015. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther,* 14**,** 341-9.

Rades, D., Huttenlocher, S., Dunst, J., Bajrovic, A., Karstens, J.H., Rudat, V. & Schild, S.E., 2010. Matched pair analysis comparing surgery followed by radiotherapy and radiotherapy alone for metastatic spinal cord compression. *J Clin Oncol,* 28**,** 3597-604.

Ralston, S.H., 1992. Medical management of hypercalcaemia. *British Journal of Clinical Pharmacology,* 34**,** 11-20.

Reiman, M.P. & Manske, R.C., 2011. The assessment of function: How is it measured? A clinical perspective. *The Journal of Manual & Manipulative Therapy,* 19**,** 91-99.

Rhudy, L., Dose, A.M., Basford, J., Griffin, J.M. & Cheville, A.L., 2015. Caregivers' attitudes toward promoting exercise among patients with late-stage lung cancer. *J Community Support Oncol,* 13**,** 392-8.

Riccio, A.I., Wodajo, F.M. & Malawer, M., 2007. Metastatic carcinoma of the long bones. *Am Fam Physician,* 76**,** 1489-94.

Richie, J.P., Catalona, W.J., Ahmann, F.R., Hudson, M.A., Scardino, P.T., Flanigan, R.C., Dekernion, J.B., Ratliff, T.L., Kavoussi, L.R., Dalkin, B.L. & Et Al., 1993. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology,* 42**,** 365-74.

Richman, E.L., Kenfield, S.A., Stampfer, M.J., Paciorek, A., Carroll, P.R. & Chan, J.M., 2011. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res,* 71**,** 3889-95.

Rief, H., Akbar, M., Keller, M., Omlor, G., Welzel, T., Bruckner, T., Rieken, S., Häfner, M.F., Schlampp, I., Gioules, A. & Debus, J., 2014a. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy- a randomized pilot trial. *Radiation Oncology,* 9.

Rief, H., Bruckner, T., Schlampp, I., Bostel, T., Welzel, T., Debus, J. & Förster, R., 2016a. Resistance training concomitant to radiotherapy of spinal bone metastases - survival and prognostic factors of a randomized trial. *Radiation Oncology,* 11.

Rief, H., Forster, R., Rieken, S., Bruckner, T., Schlampp, I., Bostel, T. & Debus, J., 2015. The influence of orthopedic corsets on the incidence of pathological fractures in patients with spinal bone metastases after radiotherapy. *BMC Cancer,* 15**,** 745.

Rief, H., Omlor, G., Akbar, M., Bruckner, T., Rieken, S., Forster, R., Schlampp, I., Welzel, T., Bostel, T., Roth, H.J. & Debus, J., 2016b. Biochemical markers of bone turnover in patients with spinal metastases after resistance training under radiotherapy--a randomized trial. *BMC Cancer,* 16**,** 231.

Rief, H., Omlor, G., Akbar, M., Welzel, T., Bruckner, T., Rieken, S., Haefner, M.F., Schlampp, I., Gioules, A., Habermehl, D., Von Nettelbladt, F. & Debus, J., 2014b. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy - first results of a randomized pilot trial. *BMC Cancer,* 14.

Rief, H., Petersen, L.C., Omlor, G., Akbar, M., Bruckner, T., Rieken, S., Haefner, M.F., Schlampp, I., Förster, R., Debus, J. & Welzel, T., 2014c. The effect of resistance

training during radiotherapy on spinal bone metastases in cancer patients - A randomized trial. *Radiotherapy and Oncology,* 112**,** 133-139.

Rief, H., Welzel, T., Omlor, G., Akbar, M., Bruckner, T., Rieken, S., Haefner, M.F., Schlampp, I., Gioules, A. & Debus, J., 2014d. Pain response of resistance training of the paravertebral musculature under radiotherapy in patients with spinal bone metastases - a randomized trial. *BMC Cancer,* 14.

Roberts, H.C., Denison, H.J., Martin, H.J., Patel, H.P., Syddall, H., Cooper, C. and Sayer, A.A., 2011. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age and ageing*, *40*(4), pp.423-429.

Rohrig, B., Du Prel, J.B., Wachtlin, D. & Blettner, M., 2009. Types of study in medical research: part 3 of a series on evaluation of scientific publications. *Dtsch Arztebl Int,* 106**,** 262-8.

Rogers, L.Q., 2010. Objective monitoring of physical activity after a cancer diagnosis: challenges and opportunities for enhancing cancer control. *Phys Ther Rev,* 15**,** 224-237.

Rosenstock, I.M. & Hochbaum, G.M., 1961. Some principles of research design in public health. *Am J Public Health Nations Health,* 51**,** 266-77.

Rummans, T.A., Clark, M.M., Sloan, J.A., Frost, M.H., Bostwick, J.M., Atherton, P.J., Johnson, M.E., Gamble, G., Richardson, J., Brown, P., Martensen, J., Miller, J., Piderman, K., Huschka, M., Girardi, J. & Hanson, J., 2006. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. *J Clin Oncol,* 24**,** 635-42.

Rush, A.J., Carmody, T.J., Ibrahim, H.M., Trivedi, M.H., Biggs, M.M., Shores-Wilson, K., Crismon, M.L., Toprac, M.G. & Kashner, T.M., 2006. Comparison of self-report and clinician ratings on two inventories of depressive symptomatology. *Psychiatr Serv,* 57**,** 829-37.

Saad, F., 2013. Bone-targeted therapy in prostate cancer. *European Journal of Cancer, Supplement,* 11**,** 257-259.

Saad, F., Lipton, A., Cook, R., Chen, Y.-M., Smith, M. & Coleman, R., 2007. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer,* 110**,** 1860-1867.

Saad, F., Kenfield, S.A., Chan, J.M., Hart, N.H., Courneya, K.S., Catto, J., Finn, S.P., Greenwood, R., Hughes, D.C., Mucci, L.A., Plymate, S.R., Pollak, M.N., Praet, S.F.E., Russell, A.P., Guinan, E.M., Blarigan, E.V., Casey, O., Buzza, M., Ryan, C.J. & Newton, R.U., 2016. Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL – MCRPC): A Movember funded multicenter, randomized, controlled phase III study. *Journal of Clinical Oncology,* 34**,** TPS5092-TPS5092.

Sabaté, E., 2003. *Adherence to Long-Term Therapies: Evidence for Action* Geneva, Switzerland: World Health Organization.

Sabino, M.A. & Mantyh, P.W., 2005. Pathophysiology of bone cancer pain. *J Support Oncol,* 3**,** 15-24.

Salakari, M.R., Surakka, T., Nurminen, R. & Pylkkanen, L., 2015. Effects of rehabilitation among patients with advances cancer: a systematic review. *Acta Oncol,* 54**,** 618-28.

Saliou, G., Kocheida El, M., Lehmann, P., Depriester, C., Paradot, G., Le Gars, D., Balut, A. & Deramond, H., 2010. Percutaneous vertebroplasty for pain management in malignant fractures of the spine with epidural involvement. *Radiology,* 254**,** 882-90.

Sallis, J.F. & Saelens, B.E., 2000. Assessment of Physical Activity by Self-Report: Status, Limitations, and Future Directions. *Research Quarterly for Exercise and Sport,* 71**,** 1-14.

Salz, T., Oeffinger, K.C., Mccabe, M.S., Layne, T.M. & Bach, P.B., 2012. Survivorship care plans in research and practice. *CA Cancer J Clin,* 62**,** 101-17.

Sandelowski, M., 2000. Focus on research methods-whatever happened to qualitative description?. *Research in nursing and health*, *23*(4), pp.334-340.

Santiago-Palma, J. & Payne, R., 2001. Palliative care and rehabilitation. *Cancer,* 92**,** 1049-52.

Santa Mina, D., Alibhai, S.M.H., Matthew, A.G., Guglietti, C.L., Steele, J., Trachtenberg, J. & Ritvo, P.G., 2012. Exercise in clinical cancer care: a call to action and program development description. *Current Oncology,* 19**,** e136-e144.

Saylor, P.J., Kaufman, D.S., Michaelson, M.D., Lee, R.J. & Smith, M.R., 2010. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. *J Urol,* 183**,** 2200-5.

Schmitz, K.H., Courneya, K.S., Matthews, C., Demark-Wahnefried, W., Galvao, D.A., Pinto, B.M., Irwin, M.L., Wolin, K.Y., Segal, R.J., Lucia, A., Schneider, C.M., Von Gruenigen, V.E., Schwartz, A.L. & American College of Sports, M., 2010. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc,* 42**,** 1409-26.

Schreuder, H.T., Gregoire, T.G. & Weyer, J.P., 2001. For What Applications Can Probability and Non-Probability Sampling Be Used? *Environmental Monitoring and Assessment,* 66**,** 281-291.

Scianni, A., Teixeira-Salmela, L.F. & Ada, L., 2012. Challenges in recruitment, attendance and adherence of acute stroke survivors to a randomized trial in Brazil: a feasibility study. *Rev Bras Fisioter,* 16**,** 40-5.

Sedgwick, P., 2014. Retrospective cohort studies: advantages and disadvantages. *Bmj*, *348*, p.g1072.

Segal, R.J., Reid, R.D., Courneya, K.S., Malone, S.C., Parliament, M.B., Scott, C.G., Venner, P.M., Quinney, H.A., Jones, L.W., D'angelo, M.E. & Wells, G.A., 2003. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol,* 21**,** 1653-9.

Segal, R.J., Reid, R.D., Courneya, K.S., Sigal, R.J., Kenny, G.P., Prud'homme, D.G., Malone, S.C., Wells, G.A., Scott, C.G. & Slovinec D'angelo, M.E., 2009. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *Journal of Clinical Oncology,* 27**,** 344-351.

Serpa Neto, A., Tobias-Machado, M., Esteves, M.A., Senra, M.D., Wroclawski, M.L., Fonseca, F.L., Dos Reis, R.B., Pompeo, A.C. & Giglio, A.D., 2012. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis,* 15**,** 36-44.

Shahinian, V.B., Kuo, Y.F., Freeman, J.L. & Goodwin, J.S., 2006. Risk of the "androgen deprivation syndrome" in men receiving androgen deprivation for prostate cancer. *Arch Intern Med,* 166**,** 465-71.

Sheill, G., Brady, L., Guinan, E., Hayes, B., Casey, O., Greene, J., Vlajnic, T., Cahill, F., Van Hemelrijck, M., Peat, N., Rudman, S., Hussey, J., Cunningham, M., Grogan, L., Lynch, T., Manecksha, R.P., Mccaffrey, J., Mucci, L., Sheils, O., O'leary, J., O'donnell, D.M., Mcdermott, R. & Finn, S., 2017. The ExPeCT (Examining Exercise, Prostate Cancer and Circulating Tumour Cells) trial: study protocol for a randomised controlled trial. *Trials,* 18**,** 456.

Sheill, G., Guinan, E., Neill, L.O., Hevey, D. & Hussey, J., 2017. Physical activity and advanced cancer: the views of oncology and palliative care physicians in Ireland. *Ir J Med Sci*.

Sheill, G., Guinan, E., L, O.N., Hevey, D. & Hussey, J., 2018. Physical activity and advanced cancer: The views of chartered physiotherapists in Ireland. *Physiother Theory Pract***,** 1-8.

Sheill G., Guinan E., Peat N, Hussey J., 2018. Considerations for Exercise Prescription in Patients with Bone Metastases: A Comprehensive Narrative Review. *PM&R*.

Sheldon, T.A., Guyatt, G.H. and Haines, A., 1998. Getting research findings into practice: When to act on the evidence. *BMJ: British Medical Journal*, *317*(7151), p.139.

Sibbald, B. & Roland, M., 1998. Understanding controlled trials. Why are randomised controlled trials important? *BMJ,* 316**,** 201.

Siddiqi, A.E., Sikorskii, A., Given, C.W. & Given, B., 2008. Early participant attrition from clinical trials: role of trial design and logistics. *Clin Trials,* 5**,** 328-35.

Silverberg, E., Boring, C.C. & Squires, T.S., 1990. Cancer statistics, 1990. *CA: a cancer journal for clinicians,* 40**,** 9-26.

Silverman, D., 2005, September. Instances or sequences? Improving the state of the art of qualitative research. In *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research* (Vol. 6, No. 3).

Skolarus, T.A., Wolf, A.M.D., Erb, N.L., Brooks, D.D., Rivers, B.M., Underwood, W., Salner, A.L., Zelefsky, M.J., Aragon-Ching, J.B., Slovin, S.F., Wittmann, D.A., Hoyt, M.A., Sinibaldi, V.J., Chodak, G., Pratt-Chapman, M.L. & Cowens-Alvarado, R.L., 2014. American Cancer Society prostate cancer survivorship care guidelines. *CA: A Cancer Journal for Clinicians,* 64**,** 225-249.

Small, E.J., 2014. Can Targeting the Androgen Receptor in Localized Prostate Cancer Provide Insights Into Why Men With Metastatic Castration-Resistant Prostate Cancer Die? *Journal of Clinical Oncology,* 32**,** 3689-3691.

Smith, H.S. & Mohsin, I., 2013. Painful boney metastases. *Korean J Pain,* 26**,** 223-41.

Smith, L., Mccourt, O., Henrich, M., Paton, B., Yong, K., Wardle, J. & Fisher, A., 2015. Multiple myeloma and physical activity: a scoping review. *BMJ Open,* 5**,** e009576.

Smith, M.R., 2004. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology,* 63**,** 742-5.

Solano, J.P., Gomes, B. & Higginson, I.J., 2006. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage,* 31**,** 58-69.

Sonmez, M., Akagun, T., Topbas, M., Cobanoglu, U., Sonmez, B., Yilmaz, M., Ovali, E. & Omay, S.B., 2008. Effect of pathologic fractures on survival in multiple myeloma patients: a case control study. *J Exp Clin Cancer Res,* 27**,** 11.

Speck, R.M., Courneya, K.S., Masse, L.C., Duval, S. & Schmitz, K.H., 2010. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv,* 4**,** 87-100.

Stefani, L., Galanti, G. & Klika, R., 2017. Clinical Implementation of Exercise Guidelines for Cancer Patients: Adaptation of ACSM's Guidelines to the Italian Model. *Journal of Functional Morphology and Kinesiology,* 2**,** 4.

Stein, K.D., Syrjala, K.L. & Andrykowski, M.A., 2008. Physical and psychological long-term and late effects of cancer. *Cancer,* 112**,** 2577-2592.

Steinberg, Susanne I. et al. (2013) "Subjective Memory Complaints, Cognitive Performance, and Psychological Factors in Healthy Older Adults." *American journal of Alzheimer's disease and other dementias* 28.8, 776–783.

Sternberg, C.N., Molina, A., North, S., Mainwaring, P., Fizazi, K., Hao, Y., Rothman, M., Gagnon, D.D., Kheoh, T., Haqq, C.M., Cleeland, C., De Bono, J.S. & Scher, H.I., 2013. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Ann Oncol,* 24**,** 1017-25.

Stevinson, C. & Fox, K.R., 2006. Feasibility of an exercise rehabilitation programme for cancer patients. *Eur J Cancer Care (Engl),* 15**,** 386-96.

Stokes, E.K., 2011. *Rehabilitation outcome measures*: Churchill Livingstone Edinburgh, Scotland.

Stone, P.C., Murphy, R.F., Matar, H.E. & Almerie, M.Q., 2008. Measuring the individual quality of life of patients with prostate cancer. *Prostate Cancer Prostatic Dis,* 11**,** 390-6.

Strasser, B., Steindorf, K., Wiskemann, J. & Ulrich, C.M., 2013. Impact of resistance training in cancer survivors: a meta-analysis. *Med Sci Sports Exerc,* 45**,** 2080-90.

Strauss, A. and Corbin, J., 1998. Basics of qualitative research: Procedures and techniques for developing grounded theory.

Surgeons, A.C.O., 2016. *The Commission on Cancer's (CoC) Cancer Program Standards: Ensuring Patient-Centered Care.* Chicago: American College of Surgeons.

Swenson, K.K., Nissen, M.J., Anderson, E., Shapiro, A., Schousboe, J. & Leach, J., 2009. Effects of exercise vs bisphosphonates on bone mineral density in breast cancer patients receiving chemotherapy. *J Support Oncol,* 7**,** 101-7.

Swenson, K.K., Nissen, M.J. & Henly, S.J., 2010. Physical activity in women receiving chemotherapy for breast cancer: adherence to a walking intervention. *Oncol Nurs Forum,* 37**,** 321-30.

Sygna, K., Johansen, S. & Ruland, C.M., 2015. Recruitment challenges in clinical research including cancer patients and their caregivers. A randomized controlled trial study and lessons learned. *Trials,* 16**,** 428.

Sylvia, L.G., Bernstein, E.E., Hubbard, J.L., Keating, L. & Anderson, E.J., 2014. Practical guide to measuring physical activity. *J Acad Nutr Diet,* 114**,** 199-208.

Taaffe, D.R., Buffart, L.M., Newton, R.U., Spry, N., Denham, J., Joseph, D., Lamb, D., Chambers, S.K. & Galvao, D.A., 2018. Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer. *BJU Int,* 121**,** 194-202.

Tannock , I.F., De Wit , R., Berry , W.R., Horti , J., Pluzanska , A., Chi , K.N., Oudard , S., Théodore , C., James , N.D., Turesson , I., Rosenthal , M.A. & Eisenberger , M.A., 2004. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *New England Journal of Medicine,* 351**,** 1502-1512.

Tariq, S. & Woodman, J., 2013. Using mixed methods in health research. *JRSM Short Reports,* 4**,** 2042533313479197.

Taylor, B. & Francis, K., 2013. *Qualitative research in the health sciences: methodologies, methods and processes*: Routledge.

Temel, J.S., Greer, J.A., Goldberg, S., Vogel, P.D., Sullivan, M., Pirl, W.F., Lynch, T.J., Christiani, D.C. & Smith, M.R., 2009. A structured exercise program for patients with advanced non-small cell lung cancer. *Journal of Thoracic Oncology,* 4**,** 595-601.

Terbizan, D.J., Dolezal, B.A. & Albano, C., 2002. Validity of Seven Commercially Available Heart Rate Monitors. *Measurement in Physical Education and Exercise Science,* 6**,** 243-247.

Thekkumpurath, P., Walker, J., Butcher, I., Hodges, L., Kleiboer, A., O'connor, M., Wall, L., Murray, G., Kroenke, K. & Sharpe, M., 2011. Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. *Cancer,* 117**,** 218-27.

Thomas, R.J., Kenfield, S.A. & Jimenez, A., 2017. Exercise-induced biochemical changes and their potential influence on cancer: a scientific review. *Br J Sports Med,* 51**,** 640-644.

Thompson, I.M., Pauler, D.K., Goodman, P.J., Tangen, C.M., Lucia, M.S., Parnes, H.L., Minasian, L.M., Ford, L.G., Lippman, S.M., Crawford, E.D., Crowley, J.J. & Coltman, C.A., Jr., 2004. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med,* 350**,** 2239-46.

Thompson, P.D., Arena, R., Riebe, D., Pescatello, L.S. & American College of Sports, M., 2013. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. *Curr Sports Med Rep,* 12**,** 215-7.

Thorne, S.E., Oliffe, J.L., Oglov, V. & Gelmon, K., 2013. Communication Challenges for Chronic Metastatic Cancer in an Era of Novel Therapeutics. *Qualitative Health Research,* 23**,** 863-875.

Thune, I. & Smeland, S., 2000. [Is physical activity important in treatment and rehabilitation of cancer patients?]. *Tidsskr Nor Laegeforen,* 120**,** 3302-4.

Titz, C., Hummler, S., Thomas, M. & Wiskemann, J., 2016. Physical exercise in advanced cancer patients undergoing palliative treatment. *Expert Review of Quality of Life in Cancer Care,* 1**,** 433-442.

Tjonna, A.E., Lee, S.J., Rognmo, O., Stolen, T.O., Bye, A., Haram, P.M., Loennechen, J.P., Al-Share, Q.Y., Skogvoll, E., Slordahl, S.A., Kemi, O.J., Najjar, S.M. & Wisloff, U., 2008. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation,* 118**,** 346-54.

Tong, D., Gillick, L. & Hendrickson, F.R., 1982. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer,* 50**,** 893-9.

Trochim, W.M. & Donnelly, J.P., 2001. Research methods knowledge base.

Trosclair, D., Bellar, D., Judge, L.W., Smith, J., Mazerat, N. & Brignac, A., 2011. Hand-Grip Strength as a Predictor of Muscular Strength and Endurance. *The Journal of Strength & Conditioning Research,* 25**,** S99.

Trost, S.G., Owen, N., Bauman, A.E., Sallis, J.F. & Brown, W., 2002. Correlates of adults' participation in physical activity: review and update. *Med Sci Sports Exerc,* 34**,** 1996-2001.

Uster, A., Ruehlin, M., Mey, S., Gisi, D., Knols, R., Imoberdorf, R., Pless, M. & Ballmer, P.E., 2017. Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial. *Clin Nutr*.

Uth, J., Hornstrup, T., Christensen, J.F., Christensen, K.B., Jorgensen, N.R., Helge, E.W., Schmidt, J.F., Brasso, K., Helge, J.W., Jakobsen, M.D., Andersen, L.L., Rorth, M., Midtgaard, J. & Krustrup, P., 2016a. Football training in men with prostate cancer undergoing androgen deprivation therapy: activity profile and short-term skeletal and postural balance adaptations. *Eur J Appl Physiol,* 116**,** 471-80.

Uth, J., Hornstrup, T., Christensen, J.F., Christensen, K.B., Jorgensen, N.R., Schmidt, J.F., Brasso, K., Jakobsen, M.D., Sundstrup, E., Andersen, L.L., Rorth, M., Midtgaard, J., Krustrup, P. & Helge, E.W., 2016b. Efficacy of recreational football on bone health, body composition, and physical functioning in men with prostate cancer undergoing androgen deprivation therapy: 32-week follow-up of the FC prostate randomised controlled trial. *Osteoporos Int,* 27**,** 1507-18.

Vainio, A., Auvinen, A. & Group, S.P., 1996. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. *Journal of pain and symptom management,* 12**,** 3-10.

Vaismoradi, M., Turunen, H. & Bondas, T., 2013. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nurs Health Sci,* 15**,** 398-405.

Vallance, J.K., Courneya, K.S., Plotnikoff, R.C., Dinu, I. & Mackey, J.R., 2008. Maintenance of physical activity in breast cancer survivors after a randomized trial. *Med Sci Sports Exerc,* 40**,** 173-80.

Van De Poll-Franse, L.V., Mols, F., Vingerhoets, A.J.J.M., Voogd, A.C., Roumen, R.M.H. & Coebergh, J.W.W., 2006. Increased health care utilisation among 10-year breast cancer survivors. *Supportive Care in Cancer,* 14**,** 436-443.

Van Den Dungen, I.A., Verhagen, C.A., Van Der Graaf, W.T., Van Den Berg, J.P., Vissers, K.C. & Engels, Y., 2014. Feasibility and impact of a physical exercise program in patients with advanced cancer: a pilot study. *J Palliat Med,* 17**,** 1091-8.

Van Waart, H., Stuiver, M.M., Van Harten, W.H., Geleijn, E., Kieffer, J.M., Buffart, L.M., De Maaker-Berkhof, M., Boven, E., Schrama, J., Geenen, M.M., Meerum Terwogt, J.M., Van Bochove, A., Lustig, V., Van Den Heiligenberg, S.M., Smorenburg, C.H., Hellendoorn-Van Vreeswijk, J.A., Sonke, G.S. & Aaronson, N.K., 2015. Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial. *J Clin Oncol,* 33**,** 1918-27.

Viswanathan, M., Ansari, M.T., Berkman, N.D., Chang, S., Hartling, L., Mcpheeters, M., Santaguida, P.L., Shamliyan, T., Singh, K., Tsertsvadze, A. & Treadwell, J.R., 2008. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville (MD).

W.K., O., 2012. *Sequencing of Novel Prostate Cancer Agents Is a Work in Progress* [online]. http://www.onclive.com/publications/obtn/2012/december-2012/sequencing-of-novel-prostate-cancer-agents-is-a-work-in-progress [Accessed 13th October 2015]

Walsh, D., Donnelly, S. & Rybicki, L., 2000a. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Supportive Care in Cancer,* 8**,** 175-179.

Walsh, J.M., Hussey, J., Guinan, E. & D, O.D., 2010. 'Pragmatic randomized controlled trial of individually prescribed exercise versus usual care in a heterogeneous cancer survivor population': a feasibility study PEACH trial: prescribed exercise after chemotherapy. *BMC Cancer,* 10**,** 42.

Wasserman, K. & Mcilroy, M.B., 1964. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *American Journal of Cardiology,* 14**,** 844-852.

Webb, J., Hall, J., Hall, K. & Fabunmi-Alade, R., 2016. Increasing the frequency of physical activity very brief advice by nurses to cancer patients. A mixed methods feasibility study of a training intervention. *Public Health,* 139**,** 121-133.

Weinstein, J.N., 1992. Differential diagnosis and surgical treatment of pathologic spine fractures. *Instructional Course Lectures,* 41**,** 301-315.

Welte, S.E., Wiskemann, J., Scharhag-Rosenberger, F., Forster, R., Bostel, T., Bruckner, T., Schlampp, I., Meyerhof, E., Sprave, T., Nicolay, N.H., Debus, J. & Rief, H., 2017. Differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastasis under concomitant radiotherapy: study protocol for a randomized pilot trial. *Trials,* 18**,** 155.

Whittemore, R., Chase, S.K. & Mandle, C.L., 2001. Validity in qualitative research. *Qualitative health research,* 11**,** 522-537.

Wilson, R.C. & Jones, P.W., 1991. Long-term reproducibility of Borg scale estimates of breathlessness during exercise. *Clin Sci (Lond),* 80**,** 309-12.

Winters-Stone, K.M., Dobek, J.C., Bennett, J.A., Maddalozzo, G.F., Ryan, C.W. & Beer, T.M., 2014. Skeletal response to resistance and impact training in prostate cancer survivors. *Med Sci Sports Exerc,* 46**,** 1482-8.

WHO, 1995. *Physical Status: the use and interprepretation of anthropometry* Geneva: W.H. Organisation.

Wolin, K.Y., Schwartz, A.L., Matthews, C.E., Courneya, K.S. & Schmitz, K.H., 2012. Implementing the exercise guidelines for cancer survivors. *J Support Oncol,* 10**,** 171-7.

Wong, C.K.H., Choi, E.P.H., Tsu, J.H.L., Ho, B.S.H., Ng, A.T.L., Chin, W.Y. & Yiu, M.K., 2015. Psychometric properties of Functional Assessment of Cancer Therapy-Prostate (FACT-P) in Chinese patients with prostate cancer. *Quality of Life Research,* 24**,** 2397-2402.

World Health Organisation. 2011. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consulation [ONILE]. Available at: http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf;

jsessionid=ADE2112ED0867D6846B7288E33CC30D2?sequence=1 [Accessed 12 September 2017].
Wooldridge, J.E., Anderson, C.M. & Perry, M.C., 2001. Corticosteroids in advanced cancer. *Oncology (Williston Park),* 15**,** 225-34; discussion 234-6.
Wu, J.S., Beaton, D., Smith, P.M. & Hagen, N.A., 2010. Patterns of pain and interference in patients with painful bone metastases: a brief pain inventory validation study. *J Pain Symptom Manage,* 39**,** 230-40.
Wu, J.S.Y., Monk, G., Clark, T., Robinson, J., Eigl, B.J.C. & Hagen, N., 2006. Palliative radiotherapy improves pain and reduces functional interference in patients with painful bone metastases: A quality assurance study. *Clinical Oncology,* 18**,** 539-544.
Yang, L. & Du, S., 2015. Efficacy and Safety of Zoledronic Acid and Pamidronate Disodium in the Treatment of Malignant Skeletal Metastasis: A Meta-Analysis. *Medicine (Baltimore),* 94**,** e1822.
Yard, S. & Nelson, K., 2013. Depression: Measurement. *In* M.D. Gellman & J.R. Turner (eds.) *Encyclopedia of Behavioral Medicine.* New York, NY: Springer New York, 564-567.
Yee, J., Davis, G.M., Beith, J.M., Wilcken, N., Currow, D., Emery, J., Phillips, J., Martin, A., Hui, R., Harrison, M., Segelov, E. & Kilbreath, S.L., 2014. Physical activity and fitness in women with metastatic breast cancer. *J Cancer Surviv,* 8**,** 647-56.
Yu, F., 2013. Improving recruitment, retention, and adherence to 6-month cycling in Alzheimer's disease. *Geriatr Nurs,* 34**,** 181-6.
Zeng, L., Chow, E., Zhang, L.Y., Culleton, S., Holden, L., Jon, F., Khan, L., Tsao, M., Barnes, E., Danjoux, C. & Sahgal, A., 2012. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. *Supportive Care in Cancer,* 20**,** 633-639.
Zimmer, P., Trebing, S., Timmers-Trebing, U., Schenk, A., Paust, R., Bloch, W., Rudolph, R., Streckmann, F. & Baumann, F.T., 2018. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. *Support Care Cancer,* 26**,** 615-624.
Zojer, N., Keck, A.V. & Pecherstorfer, M., 1999. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf,* 21**,** 389-406.
Zopf, E.M., Newton, R.U., Taaffe, D.R., Spry, N., Cormie, P., Joseph, D., Chambers, S.K., Baumann, F.T., Bloch, W. & Galvão, D.A., 2017. Associations between aerobic exercise levels and physical and mental health outcomes in men with bone metastatic prostate cancer: a cross-sectional investigation. *European Journal of Cancer Care,* 26**,** e12575-n/a.
Zore, Z., Zore, I.F., Matejčić, A., Kamal, M., Arslani, N. & Zlatarić, D.K., 2009. Surgical treatment of pathologic fractures in patients with metastatic tumors. *Collegium Antropologicum,* 33**,** 1383-1386.

9. Appendices

Appendix 1: Narrative Review Exercise and Bone Metastases

+ MODEL ARTICLE IN PRESS

PM R XXX (2018) 1-25

www.pmrjournal.org

Narrative Review

Considerations for Exercise Prescription in Patients With Bone Metastases: A Comprehensive Narrative Review

Gráinne Sheill, MSc, Emer M. Guinan, PhD, Nicola Peat, MSc, Juliette Hussey, PhD

Abstract

Metastatic disease is a frequent complication of advanced cancer, with bone representing one of the most common sites of metastatic occurrence. Patients with bone metastases receive long-term systemic treatments that have a significant attritional impact on muscle strength, fatigue, and physical functioning. Physical rehabilitation involving exercise and physical activity prescription has a considerable role in counteracting these changes; however, exercise is often perceived as a contraindication in the presence of bone metastases due to concerns about aggravating skeletal related events. This article examines the physical sequelae of bone metastases and outlines the factors for consideration with exercise prescription in metastatic bone disease, including bone health, pain levels, and oncologic treatment. This article includes a comprehensive review of the evidence from trials of exercise prescription in this population, including the efficacy and safety outcomes of exercise interventions. Exercise interventions for patients with bone metastases are associated with positive physical and self-reported outcomes. Studies reviewed reporting adverse events did not find a high fracture incidence with exercise in comparison with control participants, or an association between exercise and fracture risk. The need to individualize exercise prescription and adapt exercises to patient ability were reinforced in all papers reviewed. Exercise prescription to patients with bone metastases does involve complex decision making; however, a number of tools are available that may inform both the assessment of patients and the prescription of exercise.

Introduction

Over the past 20 years, advances in our understanding of tumor biology have led to the development of improved treatment strategies for many cancers. Advances in systemic therapies for cancer have prolonged survival even in those who cannot be cured, and many people now live with advanced stages of cancer for longer periods [1,2]. Metastatic disease is a frequent complication of advanced cancer, with bone representing one of the most common sites of metastatic occurrence [3]. The incidence of bone metastases varies with different primary cancer tumors, ranging from 14% in melanoma to 90% in multiple myeloma. In patients with breast and prostate cancer, the incidence of bone metastases ranges from 65% to 75% [4]. With increased life expectancy of this patient group, the incidences of skeletal metastasis continues to increase, with more than 1.5 million patients worldwide living with bone metastases [5].

It follows therefore that optimizing physical capacity and maintaining independence with activities of daily living in patients with bone metastases for as long as possible is essential to maximize quality of life (QoL) [6]. Patients with bone metastases receive long-term systemic treatments that have a significant attritional impact on muscle strength, fatigue, and physical functioning. Physical rehabilitation involving exercise and physical activity prescription has a considerable role in counteracting these changes, with evidence from systematic reviews of exercise interventions in patient with bone metastases reporting improvements in functional capacity, lower fatigue levels, and increased QoL [7,8].

Despite the known benefits of physical activity for patients living with cancer, exercise prescription in patients with metastatic disease is challenging. Exercise is often perceived as a contraindication in the presence of bone metastases due to concerns about aggravating skeletal-related events (SREs) [9-11]. Recent in-depth

1934-1482/$ - see front matter © 2018 by the American Academy of Physical Medicine and Rehabilitation
https://doi.org/10.1016/j.pmrj.2018.02.006

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

surveys with health care professionals (medical oncologists, radiation oncologists, palliative care physicians, and specialist physiotherapists) involved in the management of patients with bone metastases in Ireland highlighted concerns that increasing physical activity would increase risk of SREs and aggravate symptom control [12,13]. The consequences of SREs, such as pathologic fractures and extradural spinal cord compression, include severe pain, increased health care costs, reduced QoL, and increased mortality [14]. Among patients, however, interest in physical activity is high. One cross-sectional study of 50 patients living with a high burden of metastatic bone disease reported that 92% were interested in completing exercise programs and felt able to do so [15]. Despite this keen interest, exercise levels in this population are suboptimal, with only 29% of patients with bone metastases meeting the current aerobic exercise guidelines for cancer survivors [16].

This review aims to examine factors for consideration with exercise prescription in metastatic bone disease, review the evidence from trials of exercise prescription in this population, and examine the efficacy and safety outcomes of exercise interventions. The review will examine (1) the physical sequelae of bone metastases; (2) factors to consider with exercise prescription, and (3) a comprehensive review of structured exercise training in patients with metastatic bone disease (Figure 1).

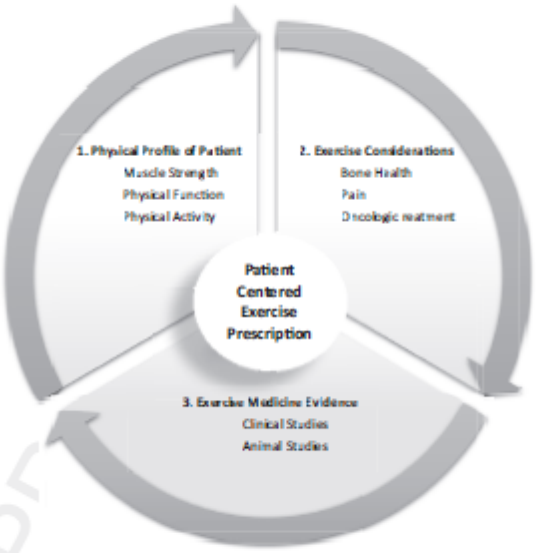


Figure 1. Exercise prescription in metastatic bone disease.

Section One: The Physical Profile of the Patient

Metastatic cancer and its associated treatment have a considerable attritional impact on multiple components of physical performance, including muscle strength, physical function, and physical activity. The following section provides an overview of the unique and multifaceted clinical profile of this patient cohort, thus outlining the challenges to be addressed by exercise rehabilitation

Muscle Strength

Skeletal muscle loss and muscle weakness are a well-described sequela of early-stage cancers [17,18]. Although less is known about skeletal muscle impairment in metastatic bone disease, sarcopenia is associated with treatment toxicity and time-to-tumor progression [19], and therefore addressing muscle loss is of considerable clinical importance. A small number of cohort studies have reported suboptimal muscle strength in patients with metastatic bone disease [20-22]. In one example in metastatic breast cancer (n = 71), both relative and adjusted grip strength (26.6 [6.0] vs 30.2 [6.4] kg, $P = .001$, and 0.38 [0.09] vs 0.46 [0.11] $kg.kg^{-1}$, $P < .001$, respectively) and leg strength [53.5 23.7] vs 76.0 [27.4] kg, $P < .001$, and 0.76 [0.31] vs 1.15 [0.45] $kg.kg^{-1}$, $P < .001$) were significant lower than matched healthy controls [23]. Hand grip strength is negatively associated with physical frailty and low scores are predictive of disability in older people [24].

In addition, measures of lower limb muscle function, such as 30-second sit-to-stand (STS) test scores, are impaired in metastatic cohorts, with patients completing approximately one half the number of STS repetitions (11.5 [4]) in comparison with matched controls (22 [7]) [22,25]. In patients with spinal metastases, preintervention data from an exercise study reported baseline STS repetitions as low as 5.1 (1.4) (intervention) and 4.6 (2.0) (control); however, this outcome was amenable to rehabilitation, with the intervention arm increasing to 9.0 (2.6) repetitions after 3 months of isometric spinal strengthening [26]. Of concern, in older healthy cohorts (>60 years old), 30-second STS <15 repetitions is predictive of falls risk and fracture risk and therefore the consequences of the low STS repetition values observed in patients with metastatic bone disease may be considerable [27].

Physical Function

Physical function involves the performance and coordination of various physiological systems, all of which may be impaired as a result of cancer treatment [28,29]. Physical function may be measured with the use of both subjective and objective physical performance measures, which show comparable levels of validity, sensitivity, and responsiveness [30,31]. Functional deficits in patients with metastatic bone disease have been reported by studies using a range of measurement methods.

Subjective measures of physical function are commonly used for patients with metastatic bone

disease, such as the physician-completed Musculoskeletal Tumor Society Score and the patient-completed Patient-Reported Outcome Measurement Information Systems Physical Function Cancer questionnaire, a superior measure of physical function in patients with lower extremity bone metastases due to its validity, brevity, and reliability over a wide range of ability levels [32]. Patients with primary cancer report a mean Patient-Reported Outcome Measurement Information Systems Physical Function (short form) score of 44.9, one half a standard deviation lower than the U.S. population mean, whereas patients with lower extremity bone metastases report lower median scores of 36 (interquartile range 31-43) [33,32], highlighting the considerable impact of bone metastases on patient-reported functional ability.

Tools that incorporate objective measures of physical function, such as the Short Physical Performance Battery and Fast Gait Speed, are predictive of premature mortality in all cancer survivors [29] and therefore have wide clinical applicability. The 6-minute walk distance (6MWD), a submaximal exercise test of aerobic capacity and endurance, examines the furthest distance that a patient can mobilize over a 30-m course during 6 minutes. In metastatic non–small cell lung cancer, one prospective study ($n = 118$) reported that 6MWD was independently predictive of survival, with patients completing <358.5 m having greater chance of all-cause mortality compared with a 6MWD of 358.5-450 m (adjusted hazard ratio 0.61 (95% confidence interval [CI] 0.34-1.07) or 6MWD >450 0.48 m (95% CI 0.24-0.93) [34].

Physical Activity

Physical activity is defined as body movement produced by skeletal muscles, which results in energy expenditure [35]. There are many health benefits associated with physical activity participation during and after cancer treatments [36]. Studies in patients with metastatic disease however, have shown that this patient group are at significant risk of low physical activity levels. In a cross-sectional study of 55 patients living with metastatic bone, 71% of participants self-reported that they were insufficiently active and did not meet the current aerobic exercise guidelines for cancer survivors [16]. When measured using objective methods, physical activity levels are considerably lower. In a cross-sectional analysis of 71 patients with metastatic breast cancer ($n = 19$ bone-only metastases), those with metastatic disease achieved only 56% of the steps completed by controls each day (5434 [3174] vs 9635 [3327] of steps/d, $P < .001$) [23]. Objectively measured physical activity levels in patients receiving radiotherapy for bone pain are comparable with physical activity levels in patients receiving chemotherapy [37]. As objective physical activity scores correlate significantly with QoL of patients with cancer, there is a need for strategies to increase physical activity levels in metastatic patients [37].

Section Two: Considerations for Exercise Prescription

All cancer survivors, including patients living with bone metastases, are advised to engage in 150 minutes of weekly moderate-intensity aerobic exercise and to include strength and flexibility training in their program [38]. For patients with bone metastases, however, achieving these guidelines may prove challenging. Even when encouraging patients to be as physically active as their abilities and conditions allow, exercise prescription is complicated by several factors associated with bone lesions including compromised bone health, risk of pathologic fracture, and increased levels of pain. Considerations for exercise prescription in the presence of these complications is considered in the sections to follow.

Bone Health

Osteoporosis

Osteoporosis and osteopenia are a common sequela for patients with bone metastases. This is due to the direct effects of cancer cells on the skeleton and to deleterious effects of cancer-specific therapies on bone cells [39]. In a case controlled analysis of 174 hormone-naive men with advanced prostate cancer, 42% were osteoporotic and 37% were osteopenic at diagnosis compared with a 27% incidence of osteoporosis amongst peer-matched controls ($P = .02$) [40]. In addition, steroid use, often used in advanced cancer for disease control and symptom management, is a strong independent risk factor for fractures [41,42].

Osteoporosis often arises as a side-effect of cancer therapies such as androgen-deprivation therapy (ADT) for prostate cancer, aromatase inhibition for breast cancer, or chemotherapy-induced ovarian failure [43]. ADT, the most commonly used therapeutic strategy for men with advanced prostate cancer, increases bone turnover and decreases bone mineral density (BMD), leading to a 20%-45% increase in relative fracture risk [44]. In addition, a large randomized study examining the effects of hormone treatment on bone health in patients with metastatic breast cancer found that, relative to baseline, endocrine therapy independently resulted in BMD declines at the lumbar spine (−11.3%) and hip (−7.3%) over 36 months [39].

Osteoporosis management involves a multimodal approach comprising pharmacologic and conservative interventions. Conservatively, education about fracture-risk activities, such as heavy lifting or high-impact activities, and prescription of individualized exercise programs for muscle strengthening and falls prevention are recommended [45]. A large retrospective study has shown

that abandoning general corset use in patients with spinal metastases does not increase rates of pathologic fracture after radiotherapy [46]. Functional loading activities such as walking exert a positive influence on bone mass [47]. Changes in bone mass occur more rapidly with unloading than with increased loading [48]. Therefore, patients with bone metastases experiencing osteopenia and osteoporosis should be encouraged to, at the very least, maintain physical activity levels for as long as possible and include suitable loading exercises to preserve bone mass.

Pathologic Fracture Risk

A fracture that develops in an area of bone pathology, such as a metastases, is termed a pathologic fracture, the consequences of which include severe bone pain, mobility limitations, and the possibility of surgery and hospitalization [49]. The incidence of pathologic fracture ranges from 43% in patients with multiple myeloma to 17% in patients with metastatic lung cancer [50]. Risk factors for pathologic fracture include the size of the lesion and increasing pain; however, little is known about the influence of physical activity on fracture rates. In one prospective study of 54 patients with bone metastases receiving inpatient rehabilitation, 16 fractures occurred in 12 patients, with only 1 fracture associated with rehabilitation [53]. Patients in the fracture group were significantly more likely to be female, younger, have a larger number of metastatic sites, and a previous occurrence of pathologic fracture [51]. In addition, lytic metastases (those that break down bone), common in myeloma or renal cell carcinoma, were more likely to develop into fractures in comparison with osteoblastic metastases (those that stimulate bone growth), common in prostate cancer. Although hypercalcemia and administration of parental narcotic suggest a poor rehabilitation outcome in those referred to rehabilitation after pathologic fracture, patients with pathologic fractures secondary to metastatic disease are considered excellent candidates for intensive exercise rehabilitation programs [52].

In recognition of the multifaceted nature of fracture risk, algorithms such as Mirels' Classification scoring system can provide a useful measure of fracture risk. This system encompasses multiple details including the site of metastases, patient-reported pain level, radiographic appearance, and size of the lesion (Table 1). All the features are assigned progressive scores ranging from 1 to 3. Based on an overall score, a recommendation for or against prophylactic fixation of a lesion is given. According to Mirels' recommendation, prophylactic fixation is highly indicated for a lesion with an overall score of 9 or greater. A lesion with an overall score of 7 or less can be managed using radiotherapy and drugs. An overall score of 8 presents a clinical dilemma. The probability of fracture is only 15%, and Mirels recommends the attending physician use clinical judgment in such cases and consider prophylactic fixation. The system has good sensitivity (91%) but relatively poor specificity (35%) [53].

Table 1
Mirels' Classification scoring system for pathologic fracture prediction

Score	1	2	3
Site	Upper limb	Lower limb	Trochanteric
Pain	Mild	Moderate	Functional
Radiographic appearance	Blastic	Mixed	Lytic
Size of lesion	<1/3 cortex	1/3-2/3 cortex	>2/3 cortex

Although not currently used widely in exercise oncology, assessing patients for risk of fracture using tools such as Mirels' criteria could form a useful basis for exercise prescription. The scoring system has the potential to be used as a decision tool for selecting patients suitable for exercise interventions and also be used as an aid the selection of participants suitable for exercise prescription (Table 2) [55]. Just one study in patients with multiple myeloma, a cohort similar to metastatic bone disease, has used Mirels' Classification to screen for fracture risk and exercise suitability. In this analysis, there were 13 (21.6%) screen failures from a total of 75 eligible participants due to fracture risk, typically large lytic lesions of the long bones or extensive lytic disease in the pelvis. Those not at risk were recommended for exercise, whereas others deemed at risk underwent cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging and were referred for surgery and/or radiotherapy before embarking on the exercise program [54].

Other fracture screening tools such as the World Health Organization screening tool (FRAX) [56] may also be useful. The FRAX calculator (www.shef.ac.uk/FRAX/) identifies 10-year fracture risk. The FRAX accounts for hormone therapy by classifying it as secondary osteoporosis and is considered superior to using measures of BMD alone to determine fracture risk [57]. A number of recent studies have investigated the value of CT based-Finite Element 3-dimensional modeling and CT-based structural rigidity analysis in predicting fractures. Both methods may considerably advance the accuracy of pathologic femur fracture prediction [58,59]; however, in clinical practice, where this level of radiologic analysis is not available, Mirels' classification can provide an extremely meaningful and cost-effective measure of fracture risk.

Pain

Bone pain is usually the earliest and most common symptom of bone metastases [60]. Up to 83% of patients with metastatic bone disease complain of cancer-induced bone pain, with wide variations in pattern and severity [61]. Incident or breakthrough pain, defined as an abrupt, short-lived, and intense flare of pain in the setting of chronic pain, may significantly impact

Table 2
Mirels' Classification and exercise prescription

Mirels' Score	Fracture Risk (%)	Treatment Recommendation	Exercise Recommendation
≥9	33-100	Prophylactic fixation is recommended.	Further medical assessment is necessary before exercise prescription.
8	15	Clinical judgment should be used.	Patient should be prescribed an individualized exercise plan.
≤7	<4	Observation and radiation therapy can be used.	Patient should be prescribed an individualized exercise plan.

Mirels' Classification is a system used to predict the greatest risk of pathologic fracture among bones affected by metastases and could also be used to identify those suitable for exercise prescription.
Adapted from Gulia et al [55].

exercise prescription [62]. The Brief Pain Inventory (BPI), which evaluates pain severity and the resulting functional interference, is a valid and reliable tool for pain measurement in patients with bone metastases [63,64]. With the use of this tool, patients with bone metastases (n = 258) report substantial pain-related interference in activity, despite the classification of pain levels as mild or moderate [64]. Therapists should be aware that unidimensional measures of pain (eg, Numerical Rating Scales) do not always correlate with physical function. Measure such as the BPI ensure both pain severity and pain interference on function are measured. Relatively mild pain intensity scores could conceal clinically important functional impairments in patients with lower body metastases, and attention to activity function is critical during assessment.

Pain associated with functional activity is associated with greater risk of pathologic fracture and hence is an integral component of risk prediction models such as Mirels' Classification. In one study of 66 consecutive patients with 100 metastases in long bones, only 6 of 57 bone lesions that were classified by patients as mildly or moderately painful later fractured; however, all lesions in which pain was aggravated by function subsequently fractured [65]. Therefore, although many of this patient group will receive regular analgesia for bone pain, those experiencing breakthrough pain, particularly associated with functional activity, should be investigated fully before commencing exercise programs. Exercise studies in patients with bone metastases monitor pain levels closely, modifying the intervention if pain increases [66]. If pain persists, orthopedic opinion may be required before the continuation of exercise and in cases of severe pain, before the patient can resume activities of daily living. Pain within the spine is also a predictor of metastatic spinal cord compression (Figure 2), which present in 83%-95% of patients at the time of diagnosis [67].

Current methods of predicting fracture risk do not consider the absolute amount of weight that is placed on the bone; however, it has been proposed that greater patient body weight leads to greater fracture risk [69]. There is uncertainty around the level of weight bearing a patient with bone metastases can be permitted. In one study of 38 patients with 78 long bone lesions, there were no differences in the rate of pathologic fracture between patients completing weight-bearing versus non–weight-bearing activity, indicating patients should be encouraged to engage in pain-free weight-bearing activity [65,70]. Conversely, pain with weight-bearing activities can indicate pathologic fracture, particularly in the lower extremities, and therefore weight-bearing activities should be avoided in the presence of pain. This further emphasizes the need to monitor pain throughout exercise sessions and modify treatments accordingly.

Oncologic Treatment

The main goal of treatment for bone metastases is to reduce the incidence of SREs and improve QoL and mobility. In addition to standard anticancer therapies such as chemotherapy and hormone therapy, modern treatment of metastatic bone disease includes analgesics, radiation therapy, surgery, and bisphosphonate drugs [71]. The following section will discuss each of these treatments, as well as describing the impact each will have on patients' physical function and performance. Physiatrists and therapists should be aware that all treatments will alter rehabilitative goals and patient suitability for particular interventions.

Analgesics

Effective analgesia is fundamental to a patients' ability to participate in exercise. Adequate pain relief significantly increases mobility and general activity in patients with bone metastases [72]. The pharmacologic approach to the treatment or palliation of painful osseous metastases follows the World Health Organization's analgesic stepladder. This "triple opioid therapy approach" involves (1) controlled-release opioids (to control background constant pain), (2) immediate-release opioids (to control gradual onset breakthrough pain), and (3) rapid-onset opioids (to control sudden increases in pain) [73]. Analgesic agents may include nonopioid analgesics (eg, nonsteroidal anti-inflammatory drugs), adjuvants (eg, antidepressants, muscle relaxants), and opioids/opioid-like analgesic agents [73]. It is particularly difficult to

Medical Emergency: Metastatic Spinal Cord Compression

- Pain, usually severe local back pain, at the level of the lesion, which progressively increases in intensity, is usually the first symptom of MSCC[66].
- The Gain Guidelines for the Rehabilitation of Patients with Metastatic Spinal Cord Compression suggest that stability of the spine and the level of mobility allowed should be agreed by the multi-disciplinary team[67].
- Clinical vigilance must be exercised with rehabilitation and exercise prescription. Any worsening of pain and neurological symptoms should be recorded, reported and medical advice sought.
- If pain or neurological symptoms worsen during rehabilitation, the activity should be stopped, and the patient returned to a spinal protective position where these changes reverse.

Figure 2. Medical emergency: metastatic spinal cord compression.

achieve pain control when bone metastases cause pain on movement [72]. Often nonsteroidal anti-inflammatory drugs and opioid analgesics are ineffective and further interventions, such as those detailed to follow, are required.

Radiation Therapy

Palliative radiotherapy can successfully relieve symptoms of advanced cancer, with the most common indication for its use being localized, uncomplicated painful bone metastases [74]. Large multi-institutional randomized trials have demonstrated that 80% of patients receiving radiotherapy for osseous metastases will experience complete-to-partial pain relief, typically within 10-14 days of the initiation therapy [75]. Pain reduction, measured with the BPI, is associated with positive changes in physical function [76]. In contrast, neither location of bone metastases nor radiotherapy dose predict pain response or functional interference following radiation treatment [77]. Studies prescribing exercise for patients receiving palliative radiation treatment report no adverse events [22,78,79]. The only documented precaution specific to exercise prescription in patients after radiotherapy is severe tissue reactions such as dryness, itching, blistering, or peeling, leading to increased risk of infection [80].

Surgical Intervention

Surgical interventions for metastatic bone lesions are completed to relieve pain or neurologic symptoms, stabilize fractures, restore function, enable ambulation, and overall increase patient QoL [3]. Pathologic fractures lead to extreme pain, urgent hospitalization, and the risk of emergency surgery with compromised outcome. Thus, predicting impending fracture and prophylactic fixation in an elective setting are critical to avoid debilitating complications. Mirels' Classification can be used to identify patients at the greatest risk of impending pathologic fracture, and several options are available for prophylactic osteosynthesis including the use of plates and screws, intramedullary nails, reconstruction nails, and endoprosthesis.

In patients who experience pathologic fracture, surgical intervention can lead to significant improvements in physical function and activity levels [81]. For example, in a study of 67 patients who underwent surgery for long bone fractures caused by metastatic tumors, significant improvements were reported in measures of activities of daily living such as washing and dressing [3]. For patients with malignant spinal tumors, percutaneous vertebroplasty and kyphoplasty are effective minimally invasive procedures that provide analgesia and spinal stabilization that restore or preserve ambulation [82-84]. Weight-bearing status may vary postoperatively depending on bone quality and types of fracture pattern as well as surgical procedure, and therefore a collaborative approach to postoperative mobilization involving the surgical and rehabilitation team is advised [85].

Bone-Modifying Agents

Bone-modifying agents have some analgesic effect and reduce the risk of SREs while reducing the need for palliative radiotherapy and surgery [86,87]. Two classes

of agents used are the bisphosphonates (pamidronate, zoledronic acid [ZA], clodronate, and ibandronate) and the RANK ligand inhibitor, denosumab [88-90]. In addition, corticosteroids (eg, Decadron) are recommended as an adjuvant analgesic for cancer-related bone pain. The mechanism of action is likely related to decreasing tumor-related edema at the site of metastases, although the evidence base largely relies on favorable clinical observations [91].

Bisphosphonates are associated with acute-phase reactions in approximately 15%-20% of patients (primarily after the first 1 or 2 infusions), which are characterized by mild-to-moderate flu-like symptoms such as low-grade fever, fatigue, arthralgia or myalgia, increased bone pain, and nausea [92]. This can begin days or months after starting treatment. Patients may require additional analgesia and adaptions to exercise programs until symptoms improve [93]. Intravenous bisphosphonates are the treatment of choice for the initial management of hypercalcemia (Figure 3) [94,95]. The effect of exercise on BMD was compared with the effects of bisphosphonates (ZA) on BMD in one randomized controlled trial. At 12 months, spine, total hip, and total body BMD increased in the ZA group by 1.6%, 0.8%, and 0.8%, respectively; however, BMD decreased in the physical activity group by 6.0%, 3.4%, and 3.3%, respectively (P values $<.0001$ for all group comparisons). ZA protected patients with breast cancer against bone loss during initial treatment, whereas home-based physical activity was less effective in preventing bone loss [96].

Section Three: Exercise Medicine Evidence

Given the potential for exercise to enhance function, ameliorate the side-effects of treatment or act as an adjunct to modern anticancer treatments, the purpose of this literature review was to comprehensively synthesize evidence on the involvement of patients with bone metastases in exercise trials. The following section summarizes the available evidence concerning exercise programs involving patients with metastatic bone disease.

Methods

Papers were identified through a search of the following databases: CINHAL, EMBASE, Medline, PubMed, SCOPUS, and Web of Science. The search terms used included combinations of physical activity or exercise and key words related to bone metastases, including "bone metastases," "spine metastasis," "advanced cancer," "advanced neoplasm," "bone neoplasms," "spinal neoplasms," "pelvic neoplasms," "spine metastases," "spontaneous fracture," "pathologic fracture," "bone pain," and "fragile bone." In addition, studies retrieved from journal publication reference lists, and any other published studies known to the authors were also included. The search included the literature up to October 2017. No limits were applied to the searches.

Studies that involved patients with metastatic disease, in particular bone metastases, as a result of solid primary tumors, participating in supervised exercise interventions were eligible for inclusion. When it was unclear whether patients with bone metastases were included or were eligible for inclusion, the authors of the paper were contacted for clarification. The results of the literature search were screened by 2 authors for inclusion in the current review. A flow diagram of the literature search and selection is presented in Figure 4. Details relating to exercise programs prescribed, adverse events, and outcomes related to physical

Medical Emergency: Hypercalcemia

- Hypercalcaemia is an abnormally large amount of calcium in the blood which affects up to 10% of patients with advanced cancers.
- The clinical features of hypercalcemia include neurological changes, cognitive changes, gastrointestinal, renal and cardiovascular symptoms.
- Asymptomatic or mildly symptomatic individuals with hypercalcemia may not require immediate therapy. However, hypercalcemia with malignancy usually presents with markedly elevated calcium levels (>3.5 mol/L) and therefore is usually severely symptomatic and is considered on oncological emergency.

Figure 3. Information on hypercalcaemia of malignancy, adapted from Mirrakhimov [95].

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

activity, physical function, and QoL were extracted from studies.

Given the complexity of biological systems, the use of animal models has provided a significant understanding of the various adaptive mechanisms undergoing acute and chronic physical exercise [97]. Studies examining the effect of exercise training in animal models with metastatic bone disease were also included.

Results of Literature Review

Eleven studies, described in 18 papers, relating to exercise prescription in patients with bone metastases were considered eligible for inclusion; 7 randomized controlled trials, 3 single-arm studies and 1 multiarm interventional study (Table 3) [~~13~~,14,25,29,67,79,80,97-106,~~124~~]. Aerobic and/or resistance exercise training was prescribed by all studies. Five studies examined aerobic and resistance training as a multimodal intervention, and 1 study compared an aerobic training intervention to a resistance training intervention. In addition, 3 studies prescribed resistance training only, whereas 2 studies prescribed aerobic training only. Studies in animals included for review prescribed aerobic exercise or lower limb training interventions.

All studies reviewed included patients with metastatic bone disease. In 6 studies, participants had a diagnosis of primary prostate cancer, whereas 4 studies included participants who had a mix of primary cancer diagnoses. One study included only patients with metastatic breast cancer. In total, studies involved 593 patients with metastatic disease, of which 347 were prescribed exercise. The remaining 246 patients served as control subjects. Participant age ranged from 49 to 73.1 years and BMI ranged from 26.6 to 29.3kg/m^2.

Aerobic Exercise

Two studies reviewed prescribed aerobic exercise as a uni-modal intervention. The first prescribed a 12-week RCT of football training program for men undergoing ADT for advanced or locally advanced prostate cancer ($n = 57$), 11 of whom had metastatic bone disease [98]. The football program consisted of 15 minutes of warm-up exercises (running, dribbling, passing, shooting, balance, and muscle strength exercises) followed by 2×15 minutes of 5- to 7-a-side games. The football training group ($n = 29$) practiced 2-3 times per week for 45-60 minutes, whereas a standard-care control group ($n = 28$) was instructed to maintain their baseline activity levels. Postintervention, the football group demonstrated

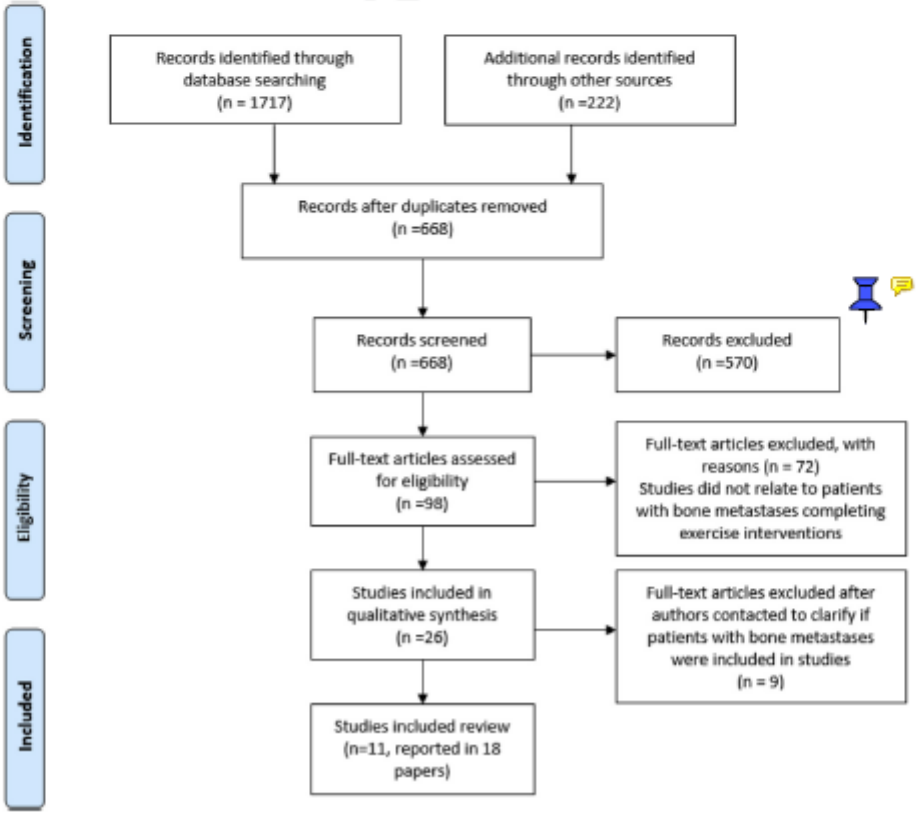


Figure 4. Comprehensive literature search strategy.

Table 3
Exercise interventions for patients with bone metastases: Research studies included in this review

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
Bourke et al, 2011 [105]	Intervention, n = 6/25 (24%) Control, n = 7/25 (28%)	12 weeks of aerobic and resistance exercise F: Weeks 1-6: Twice weekly Weeks 6-12: Once weekly I: 55%-85% of age-predicted maximum HR and/or RPE 11-15 T: 30 minutes of aerobic exercise and between 2 and 4 sets of resistance exercises T: Aerobic: Not specified Resistance: Body weight resistance and free weights Home exercise component: Yes Self-directed exercise (eg, brisk walking, cycling, and gym exercise) for at least one 30-minute session per week during the initial 6 weeks and at least 2 sessions per week for the final 6 weeks.	Not reported	Attendance at supervised exercise sessions: 360/378 sessions (95%) Compliance to the self-directed exercise: 329/378 sessions (87%) (ie, patients reporting at least 25-30 minutes of aerobic exercise in log books)	Significant change reported in: Total exercise behavior (GLSIQ) Postintervention Intervention 33.8 vs control 17.4 Godin LSI points (mean difference 16.3, 95% CI 8.8-23.8; $P < .001$) 6-month follow-up Intervention 25.9 vs control 15.6 Godin LSI points (mean difference 11.3, 95% CI ¼ 5.0-17.5; $P = .001$) Fatigue (FACT-F) Postintervention Exercise (44 [6] to 48 [4]) points Control (43 [8] to 42 [8]) points (mean difference 5.4, 95% CI 0.8-10.0; $P = .002$) 6-month follow-up Exercise 48 (4) to 43 (7) points Control 42 (8) to 40 (8) points (mean difference 3.1, 95% CI 0.3-6.4; $P =. 006$) Exercise tolerance (Bruce Protocol) Postintervention Exercise (351.1 [110.8] to 495.8 [125.0] s) Control (368.6 [129.1] to 379.8 [129.2] s) (Mean difference 133.4, 95% CI 92.4-174.4; $P < .001$) 6-month follow-up Exercise 495.8 (125.0) to 435.8 (118.5) s Control 379.8 (129.2) to 351.0 (114.4) s (mean difference 102.2, 95% CI 56.8-147.6; $P < .001$) Functional fitness (30-second chair sit to stand) Postintervention Exercise (11.1 [2.3] to 16.0 [3.7] reps) Control (12.3 [3.7] to 13.4 [4.3] reps) (mean difference 3.79, 95% CI 1.68-5.90; $P = .002$) 6-month follow-up Exercise (16.0 [3.7] to 16.1 [4.1] reps) Control (13.4 [4.3] to 13.6 [3.8] reps)

(*continued on next page*)

Table 3 (*continued*)

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
					(mean difference 3.66, 95% CI 1.71-5.6; $P = .001$) Muscle strength (maximum voluntary torque) Postintervention Exercise (181.9 [42.7] to 190.3 [40.9] kg) Control (170.8 [52.0] to 169.2 [48.8] kg) (mean difference 9.97, 95% CI −0.92 to 20.8; $P = .033$) 6-month follow-up Exercise (190.3 [40.9] to 195.5 [43.6] kg) Control (169.2 [48.8] to 176.2 [53.8] kg) (Mean difference 8.20, 95% CI −0.90 to 17.3; $P = .035$) No change reported in Quality of life At end of intervention; $P = .21$ (FACT-P) and $P = .25$ (FACT-G), or at 6 months ($P = .45$ and $P = .36$). Anthropometric variables At end of intervention; $P = .20$ (weight), $P = .76$ (BMI), $P = .39$ (waist-hip ratio) or at 6 months $P = .27$ (weight), $P = .88$ (BMI) or $P = .56$ (waist-hip ratio).
Bourke et al, 2014 [106]	Intervention, n = 11/50 (22%) Control, n = 9/50 (18%)	12 weeks of aerobic and resistance exercise with parallel dietary advice. F: Weeks 1-6: Twice weekly Weeks 6-12 once weekly I: Aerobic: 55%-75% of age-predicted maximum HR and/or RPE 11-13. Resistance: 60% of 1RM progressed by volume and weight T: 30 minutes of aerobic exercise and between 2 and 4 sets and 8–12 reps of resistance exercises T: Aerobic: stationary cycles, rowing ergometers and treadmills. Resistance: Body weight resistance and free weights Home exercise component: Yes	n = 1 atrial fibrillation n = 1 death in the usual-care arm during the intervention. There were no skeletal-related adverse events during follow-up.	Adherence was 94% for the supervised and 82% of the prescribed independent exercise sessions.	Significant change reported in: Quality of life at 3 months (FACT-P) (adjusted mean group difference: 8.9; 95% CI 3.7-14.2; $P = .001$) Exercise tolerance (Bruce Protocol) (adjusted mean group difference: 121.2 s; 95% CI 91.6-150.8; $P < .001$) Fatigue (FACT-F) (adjusted mean group difference: 5.3; 95% CI 2.7-7.9; $P < .001$) Total exercise behavior (GLSIQ) Postintervention Adjusted mean group difference: 14.6 Godin LSI points; 95% CI 7.8-21.4; $P < .001$. 6-month follow-up Adjusted mean group difference: 8.0 Godin LSI points; 95% CI 0.5-15.6; $P = .038$. No change reported in: Quality of life at 6 months (FACT-P) Adjusted mean group difference: 3.3; 95% CI S2.6-9.3; $P = .27$ at 6 months.

		At least one self-directed independent session for at least 30 minutes using the skills taught in the supervised sessions (eg, Borg). This increased to twice per week during weeks 7–12.			BMI End of intervention Adjusted mean group difference: 0.1 95% CI −0.5 to 0.7%; $P = .71$ At 6 months Adjusted mean difference: −0.5; 95% CI −1.2 to 0.2; $P = .15$
Cormie et al, 2013 [14]	Intervention, n = 20 (100%)	12-week resistance exercise program. F: Twice weekly I: progressed from 12 to 8 RM with 2-4 sets per exercise T: Aerobic exercise: Resistance exercise: 60 minutes 2 and 4 sets and 8–12 repetitions of resistance exercises T: Eight exercises that targeted the major muscle groups 10-12 Home exercise component: Yes Participants were encouraged to supplement the resistance exercise sessions with home-based aerobic exercise sessions involving walking and/or stationary cycling, with the aim of accumulating a total of at least 150 min of moderate-intensity aerobic exercise each week.	No adverse events or skeletal complications occurred during the exercise sessions. There was no between-group difference in the total number of adverse events that occurred throughout the intervention period. One incident was reported outside of the exercise sessions, in which a participant in the exercise group fell while dressing at home and suffered a rib #. Participant continued the intervention with a modified exercise program.	An average attendance of 20 sessions out of a possible 24 (83% attendance) Compliance to the exercise prescription was 93.2 ± 6.3%.	Significant change reported in: Pain (VAS, FACT-BP) No change in the use of pain medication throughout the intervention. The severity of bone pain was a maximum of 1.4±1.2 out of ten across all sessions. Exercise tolerability (RPE) Average perceived exercise intensity of 13.8 ± 1.5 Average perceived tolerance score of 6.1 ± 0.7 out of a possible rating of 7 for sessions Maximal muscular strength (1 RM leg extension) Postintervention Exercise 76.2 (17.6) to 80.3 (16.7) kg Control 71.4 (23.5) to 68.7 (21.4) kg (Adjusted mean group difference 7.9, 95% CI 1.8-4.0; $P = .016$) Submaximal aerobic exercise capacity (400-m walk) Postintervention Exercise 252.1 (40.8) to 246.9 (32.9) s Control 280.8 (53.0) to 286.5 (50.5) s (Adjusted mean group difference -13.7, 95% CI −23.5 to −3.9; $P = .010$) Ambulation (usual and fast pace 6-m walk) Postintervention Exercise 4.48 (0.54) to 4.23(0.33) s Control 4.45 (0.56) to 4.76 (0.42) s (Adjusted mean group difference -0.55, 95% CI −0.78 to −0.32; $P < .001$) Self-reported PA (low intensity activity only) (GLSIQ) Postintervention Exercise 341.7 (143.3) to 356.7 (112.6) Control 359.6 (140.7) to 316.8 (121.4) (Adjusted mean group difference 82.5, 95% CI 31.8-133.2; $P = .003$) No change reported in: Balance (SOT) (Adjusted mean group difference −1.0, 95% CI −3.4 to 1.3; $P = .362$)

(continued on next page)

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

Table 3 (*continued*)

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
					Balance confidence (The Activities-Specific Balance Confidence scale) (Adjusted mean group difference 2.4, 95% CI −13.2 to 17.8; P =.752) Fatigue (Multidimensional Fatigue Symptom Inventory-Short Form) (Adjusted mean group diff = −4.2 95% CI −17.6 to 9.2, P =.521) Quality of life Psychological distress
Cormie et al, 2014 [67]	Intervention, n = 20 (100%)	12-week resistance exercise program. F: Twice weekly I: progressed from 12 to 8 RM with 2-4 sets per exercise T: Aerobic exercise: Resistance exercise: 60 minutes 2 and 4 sets and 8−12 repetitions of resistance exercises T: ~~Eight~~ exercises that targeted the major muscle groups 10-12 Home exercise component: Yes Participants were encouraged to undertake home-based aerobic exercise sessions of walking and/or stationary cycling, with the aim of accumulating a total of 150 minutes of moderate intensity aerobic exercise each week	No adverse events occurred during the supervised resistance exercise sessions. Three participants experienced an SRE during the study period that required them to withdraw from the program, n = 2 due to bone pain and n = 1 vertebral #. Two falls were reported outside of the supervised exercise sessions. n = 1 while participant was dressing (# rib) n = 1 while walking (no skeletal complications occurred). Both participants continued the exercise intervention	Average attendance rate of 85% (~20 out of a possible 24 sessions). Compliance to the exercise prescription was high (~89 % of attended sessions).	Significant change reported in: Pain (VAS) There were no significant changes in bone pain between baseline, postexercise, and 6-month follow-up assessment points Exercise Tolerability (RPE) Average perceived intensity of 13.7 ± 1.2 on the RPE scale Average perceived tolerance score of 6.1 ± 0.7 of a possible 7 Muscle strength at 3 months (1 RM leg extension) Postintervention 70.8 (18.8) to 73.5 (18.9) kg (mean difference 2.7, 95% CI 1.0-4.5; P = .005) Aerobic capacity at 3 months (400-m walk) Postintervention 262.6 (43.6) to 255.4 (43.4) s (mean difference −7.2, 95% CI −12.0 to −2.3; P = .007) Ambulation at 3 and 6 months (usual and fast pace 6-m walk) Postintervention 4.59 (0.45) to 4.32 (0.37) s (mean difference −0.27, 95% CI −0.39 to −0.15; P < .001) At 6-month follow-up 4.32 (0.37) to 4.40 (0.51) s (mean diff = -0.19, 95% CI −0.38 to 0.00; P = .046) Self-reported PA levels at 3 months (GLSIQ) Postintervention 18.6 (14.7) to 30.5 (22.1) (mean diff = 12.0, 95% CI 5.6-18.3; P = .001)

REV 5.5.0 DTD ■ PMRJ2060 proof ■ 9 March 2018 ■ 1:39 am ■ ce

					Hip BMD at 6 months At 6-month follow-up 0.808 (0.123) to 0.824 (0.126) g/cm^2 (mean diff = 0.016, 95% CI 0.008-0.025; $P = .001$) Whole body lean mass at 3 and 6 months Postintervention 52.9 (9.9) to 54.5 (9.4) kg (mean diff = 1.5, 95% CI 0.1-2.9; $P = .039$) At 6-month follow-up 54.5 (9.4) to 53.6 (9.7) kg (Mean diff = 0.8, 95% CI 0.1-1.5; $P = .039$) No change reported in: Muscular power (TUG) Adjusted mean difference: −0.26; 95% CI −0.62 to 0.10; $P = .147$ at 12 weeks, adjusted mean difference: 0.03; 95% CI −0.55 to 0.61; $P = .915$ at 6 months. Balance confidence (The Activities-Specific Balance Confidence scale) Adjusted mean difference: 3.7; 95% CI −0.7 to 8.2; $P = .095$ at 12 weeks, adjusted mean difference: 0.01; 95% CI −3.3 to 3.6; $P = .939$ at 6 months.
Galvão et al, 2017 [104]	Intervention, n = 28 (100%) Control, n = 29 (100%)	3-month supervised multimodal exercise intervention F: Three times per week I: Res: moderate intensity (10- to 12-RM) for 3 sets per exercise. Aerobic: 60%-85% of estimated maximum heart rate Flex: 2-4 reps with 30-60 second hold T: 60 minutes Aerobic: (20-30 minutes) Ty: Res: major trunk, upper and lower body muscle groups Aerobic: walking on a treadmill, cycling or rowing on a stationary ergometer Flex: all major joints considered important for maintaining function Home exercise component: No	No exercise-related adverse events or skeletal fractures.	Participants completed a mean of 32 ± 10 of the 36 exercise sessions (89%)	Significant change reported in: Pain (Common Terminology Criteria [CTC]) Pain on the CTC pain grade (0-3 scale) was 0.2 ± 0.3. There were no changes in bone pain assessed by the FACT-BP ($P = .507$) Self-reported physical function (Short-Form 36 questionnaire) Postintervention Exercise 47.8 (6.8) to 49.5 (5.0) Control 45.5 (8.2) to 44.8 (7.8) (Mean difference 3.2, 95% CI 0.4-6.0; $P = .028$) Muscular strength (1 RM leg extension and chest press) Postintervention Exercise 60.5 (16.2) to 65.8 (14.4) kg Control 58.7 (15.8) to 57.8 (14.1) kg (Mean difference 6.6, 95% CI 0.6-12.7; $P = .033$) No change reported in: Objective measures of physical function 6MWT (adjusted mean change 0.2, 95% CI −0.1 to 0.4; $P = .192$)

(continued on next page)

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

Table 3 (*continued*)

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
					400-m walk (adjusted mean change −1.6, 95% CI −8.7 to 5.5, $P = .641$) TUG (adjusted mean change 0.1 95% CI −0.3 to 0.6, $P = .497$) Balance (SOT) Adjusted mean change 0.7, 95% CI −2.5 to 3.9, $P = .649$) Whole body lean mass (DXA) Adjusted mean change 0.3, 95% CI -1.3 to 0.7, p=.584 Fatigue (FACIT-F) ($P = .964$)
Ligibel et al, ~~2016~~ [97]	All patients (n = 101) had metastatic disease; however, it was unclear the percentage of patients who had bone metastases Intervention, n = 48 Control, n = 53	16-week aerobic exercise program F: Weeks 1-4: Supervised once weekly. Weeks 4-16 Supervised once monthly, supplemented with weekly phone calls. I: Moderate intensity measured with heart rate monitor, no further detail given. T: 150 minutes a week Ty: Access to local gym was provided, no further information given.	No injuries or other adverse events were reported in intervention or control participants.	Not reported.	No change reported in: Global QOL (EORTC QLQ-C30) (Mean change in intervention vs control: 6.0 (17.5) vs −1.0 (21.5); $P = .17$) Physical Functioning (Physical Functioning subscale of the EORTC QLQC30) (Mean change in intervention vs control group: 4.79 vs 0.93; $P = .23$) Cardiorespiratory fitness (modified Bruce Ramp Treadmill test) (Mean change in intervention vs control group 0.61 vs 0.37 minutes ($P = .35$). PA levels (7-day PA recall interview) (mean change in intervention vs control group 62.4 ± 102.8 minutes per week versus 46.0 6 ± 154.3 minutes per week ($P = .17$). Fatigue (FACIT-F) (Mean change in intervention vs control group −3.8 vs 1.6 minutes ($P = .68$).
Litterini et al, 2013 ~~[79]~~	Intervention, n = 66 (100%)	Ten weeks of individualized resistance or cardiovascular exercise. F: Twice weekly I: 10-12 (or fairly light) on the Borg Rating RPE, progressed as tolerated. Resistance: All participants started with 1 set of 8 to 15 repetitions. T: 30-60 minutes Ty: Circuit weight training equipment Home exercise component: No	No adverse events were reported.	On average, participants attended 14 (70%) of 20 exercise sessions.	Significant change reported in: Functional mobility (SPPB total score) Postintervention Cardiovascular group: 9.77 (2.25) to 10.45 (2.05) (Mean difference 1.07, 95% CI 0.57-1.58) Resistance Group: 9.38 (2.10) to 9.91 (1.95) (Mean difference 0.43, 95% CI 0.09-0.77) Total sample: 9.55 (2.16) to 10.33 (1.82) (Mean difference 0.75, 95% CI 0.44-1.06; $P < .001$ Fatigue Postintervention Cardiovascular group: 31.06 (27.4) to 26.17 (21.81) mm

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

					(mean difference 4.93, 95% CI −8.34 to 18.20) Resistance group: 42.62 (29.96) to 31.35 (24.35) mm (mean difference 13.13, 95% CI −0.76 to 25.51) Total sample: 37.02 (28.93) to 28.46 (22.28) mm (mean difference 9.03, 95% CI −0.02 to 18.08; $P = .050$) No change reported in: Balance subscores of the SPPB Total sample: 3.67(0.65) to 3.82 (0.52) (mean difference 0.16, 95% CI 0.02-0.34; $P = .090$)
Oldervoll et al, 2011 [25]	Intervention, n = 114 (94%) Control, n = 104 (94%)	8-week cardiovascular and resistance exercise F: Twice weekly I: Not described T: 50-60 minutes − warm up and 2-minute stations with a 1-minute interval in which the patients moved to the next station, continuing for 30 minutes in total. Ty: 6 circuit stations. Home exercise component: No	No exercise-related minor or serious adverse events, such as cardiovascular events or falls with fractures, were reported during or immediately after the sessions.	The adherence rate for the participants in the exercise group who completed the pre- and post-tests was, on average, 69% (11 of 16 scheduled sessions).	Significant changes reported in: Functional capacity (SWT) Exercise (339 (17.1) to 380 (24.2) m) Control (390 (17.8) to 369 (21.5) m) (Mean difference 60, 95% CI 16.0-103.4; $P = .008$) Grip strength test (dynamometer) Exercise (26.4 [0.85] to 27.5 [0.95] kg) Control (29.6 [0.94] to 28.3 [0.97] kg) (Mean difference 2.0, 95% CI 0.4-3.5; $P = .01$) Body weight Exercise (70.5 [16.3] to 73.0 [17.9] kg) Control (73.8 [17.6] to 73.0 [17.9] kg) (Mean difference 1.3, 95% CI 0.3-2.3; $P = .01$) No change reported in: Total fatigue (Fatigue Questionnaire) Exercise (18.1 (0.48) 16.8 (0.60)) Control (18.0 (0.58) to 17.2 (0.62)) (Mean difference -0.5, 95% CI −2.0 to 1.0; $P = .53$) Median survival times Exercise group: 11.1 months (95% CI 8.1−14.0 months) Control group 12.3 months (95% CI 8.0−16.5 months) ($P = .18$). Sit to stand Exercise (10.9 (0.32) to 11.7 (0.47)) Control (11.6 (0.38) to 11.9 (0.48) (Mean difference 0.5, 95% CI −0.5 to 1.5; $P = .34$)

(continued on next page)

REV 5.5.0 DTD ■ PMRJ2060_proof ■ 9 March 2018 ■ 1:39 am ■ ce

Table 3 (*continued*)

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
Porock et al, 2000 [13]	Intervention, n = 7 reported metastatic spread (78%)	2-week cardiovascular and resistance exercise Exercise was prescribed by finding out how much activity the patient could comfortably tolerate, then instructing pts to begin with half that much several times daily, with rest periods between. Patients were given a range of activities to be carried out throughout the day. Home exercise component: Yes, weekly physiotherapy visits were supplemented with home exercise programs.	No adverse events were reported		A case study analysis of participants was completed. Nonsignificant changes were reported in fatigue (multidimensional Fatigue Inventory), anxiety and depression ratings (HADS). and symptom distress rating scales.
Rief et al [29,80,100-103]	Intervention, n = 30 (50%) Control, n = 30 (50%)	12-week isometric resistance training of paravertebral muscles. F: 5 days a week (Monday to Friday) for 2 weeks Three times a week for an additional 10 weeks I: Not described T: 30 minutes Ty: Paravertebral muscle Training Home exercise component: No	No adverse events reported	Not reported	Significant change reported in: Psychosocial aspects of quality of life (EORTC QLQ-BM22) Postintervention Exercise group: 69.26 (17.0) to 45.56 (19.71) Control 57.59 (19.87) to 54.55 (20.9) (treatment effect after 3 months $P = .001$) At 6 months' follow-up Intervention 45.56 (19.71) to 41.05 (19.1) Control 54.55 (20.9) to 50.93 (20.55) (treatment effect after 6 months $P = .010$) Physical fatigue at 6 months (EORTC QLQ-FA13) At 6 months' follow-up Exercise group: 57.22 (29.0) to 35.65 (25.37) reps Control 58.06 (29.1) to 64.91 (31.25) (treatment effect after 6 months $P = .013$) reps Chair stand test at 3 months Exercise group: 5.1 (1.4) to 9.0 (2.6) Control 4.6 (2.0) to 5.0 (2.7) (Treatment effect within groups at 3 months p<.001 (intervention) $P = .525$ (Control) Treatment effect between groups $P < .001$ Pain OMED ($P = .018$) Intervention 56.8 (132.2) to 20.8 (46.9) at 6 months Control 45.0 (86.2) to 76.7 (103.6) at 6 months VAS ($P < .001$)

					Intervention 48.2 (20.5) to 16.7 (14.8) at 6 months Control 51.3 (26.9) to 50.3 (22.8) at 6 months No change reported in: Neuropathic pain (VAS) Intervention 0.2 (0.4) to 0.2 (0.4) at 6 months Control 0.2 (0.4) to 0.2 (0.4) at 6 months (Between-group change $P = .694$) Emotional fatigue (EORTC QLQ-FA13) Intervention 46.67 (32.5) to 27.31 (27.54) at 6 months Control 44.44 (30.27) to 46.05 (33.26) at 6 months (Between-group change $P = .156$) Overall survival Intervention: 88.6 months, six-month survival 90%, and 12-month survival 83.1%. Control: 72 months, and 6-month survival 96.6% and 12-month survival 78.6%, ($P = .626$). Incidence of pathologic fractures Intervention n = 5, Control n = 6 at 3 months ($P = .592$) Intervention n = 3,Control n = 5 at 6 months ($P = .604$)
Uth et al, 2016 [98,99,124]	Intervention, n = 7 (24.1%) Control, n = 4 (15.4%)	12 weeks football training F: Weeks 1-8: Twice weekly Weeks 9-12: Three times weekly Weeks 13-32: Twice weekly I: T: Weeks 1-4: 15minutes warm up, 2x15 mins games Weeks 5-32: 15minutes warm up, 3 x 15-minutesgames Ty: 5- to 7-a-side Football training Home exercise component: No	Two participants sustained a fibula fracture and three participants had muscle or tendon injuries due to the football training. No bone metastases were present in the fractured bones, these injuries were regarded as accidental and unrelated to metastatic disease.	12 weeks of the intervention period: exercise participants attended 76.5 % (SD 24.2) of the training sessions or 1.6 (SD 0.5) training sessions/week. Participants attended 46.2 % (SD 23.2) of the training sessions between week 12 and 32 or 0.9 (SD 0.5) training sessions/week	Significant change reported in: Total bone mineral content (DXA) Postintervention Exercise 3000.5 (364.4) to 3002.2 (360.8) g Control 3126.3 (452.2) to 3101.7 (445.7) g (mean difference 26.4.8, 95% CI 5.8-46.9; $P = .013$) Leg bone mineral content (DXA) Postintervention Exercise 1149.0 (143.1) to 1154.8 (145.5) g Control 1206.9 (193.8) to 1198.9 (191.5) g (Mean difference 13.8, 95% CI 7.0-20.5; $P > .001$) Lean mass (DXA) Postintervention Exercise 53.1 (5.9) to 54.0 (5.2) kg Control 56.7 (5.5) to 56.8 (5.1) kg (Mean between group diff = 0.7, 95% CI 0.1-1.2; $P = .02$) Muscle strength (knee extension 1RM) Postintervention Exercise 62.8 (15.0) to 71.7 (18.8) kg Control 71.7 (16.9) to 73.9 (16.0) kg (mean between group difference 6.7, 95% CI 2.8-10.7; $P < .001$)

(continued on next page)

Table 3 (*continued*)

	Metastatic Bone Disease Patients, n (% of Overall Study Population)	Intervention	Adverse Events	Adherence/Compliance	Results, Mean (SD)
					No change reported in: Exercise tolerance (VO2max) Postintervention Exercise 27.2 (4.6) to 28.7 (5.2) (mL O_2/kg/min) Control 26.4 (3.4) to 26.9 (3.0) (mL O_2/kg/min) Mean group difference 0.7, 95% CI −0.6 to 2.0; $P = .29$ Sit-to-stand Postintervention Exercise 20.0 (6.0) to 21.5 (6.3) reps Control 22.1 (4.9) to 22.3 (5.5) reps Mean group difference 1.2, 95% CI −0.3 to 2.8; $P = .11$ Fat mass (DXA) Exercise 27.6 (7.5) to 26.3 (7.0) kg Control 30.0 (7.7) to 29.7 (6.2) kg Mean group difference −0.6, 95% CI −1.5 to 0.2; $P = .14$ Balance test (Flamingo Balance Test) Exercise 13.8 (7.5) to 11.8 (8.0) n Control 14.5 (6.3) to 12.6 (7.1) n Mean group difference −0.0, 95% CI −2.9 to 2.8; $P = .97$

F = frequency; I = intensity; T = time; HR = heart rate; RPE = rate of perceived exertion; GLSIQ = Godin Leisure Score Index Questionnaire; LSI = Leisure Score Index; FACT-F = Functional Assessment of Cancer Therapy: Fatigue; FACT-P = Functional Assessment of Cancer Therapy: Prostate; FACT-G = Functional Assessment of Cancer Therapy: General; FACT-BP = Functional Assessment of Cancer Therapy: Bone Pain; VAS = Visual Analog Scale; SOT Sensory Organization Test; PA = physical activity; BMD = bone mineral density; TUG = Timed up and Go; RM = repetition max; BMI = body mass index; # = fracture; Ty = type of exercise; 6MWT = 6-minute walk test; DXA = dual-energy X-ray absorptiometry; FACIT-F = Functional Assessment of Chronic Illness Therapy: Fatigue; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SPPB = Short Physical Performance Battery; SWT = shuttle walk test; HADS = Hospital Anxiety and Depression Scale; OMED = oral morphine–equivalent dose; VO2max = maximum rate of oxygen consumption.

significantly greater total body bone mineral content (between-group difference 26.4 [95% CI 5.8-46.9 g; $P = .013$), leg bone mineral content (13.8 [95% CI 7.0-20.5 g; $P < .001$]), and markers of bone formation in comparison with the control group. Similarly, knee extensor strength (1RM) was significantly greater in the football group post-intervention (6.7 kg [95% CI 2.8-10.7; $P < .001$]). There were no differences in aerobic fitness or body fat percentage [99]. In relation to adverse events, 2 fibular fractures were reported in the football group; however, they did not involve patients with bone metastases and were considered as accidental and unrelated to metastatic disease [100].

The second intervention prescribed a 16-week program of moderate intensity exercise in patients with metastatic breast cancer [98]. Participants were randomized to either an intervention arm (n = 48) or a waiting-list control group (n = 53). The intervention group completed individual exercise sessions at a local gym, with a target weekly exercise goal of 150 minutes of moderate-intensity exercise. In contrast to the prostate study described previously, this training program did not result in improvements in weekly exercise, physical functioning or aerobic fitness.

Resistance Exercise

Three studies reviewed prescribed resistance exercise as a uni-modal intervention. Cormie et al [11,66] examined the feasibility of resistance exercise interventions for patients with metastatic bone disease in 2 papers, a RCT and single-group interventional study. In the RCT, 20 men with established bone metastases secondary to prostate cancer were randomly assigned to either a 12-week resistance exercise program (n = 10) or usual-care group (n = 10). Participants had significant disease load with 65% of participants presenting with 2 or more regions affected by bone metastases. By the use of a standardized approach, exercise was prescribed to avoid loading bones and minimize sheer forces on areas of the body with metastatic lesions (Table 4).

Exercise prescribed using this approach was well tolerated and did not increase the incidence of skeletal complications. Postintervention muscle strength, measured by leg extension 1RM, was significantly greater in the intervention group with a mean adjusted between-group difference of 7.6 kg ($P = .016$) immediately postintervention. Submaximal exercise capacity and ambulation speed was also greater in the intervention arm, with a post-intervention between-group difference of −13.7 seconds in a 400-m walk ($P = .010$) and a mean group difference of −0.55 seconds in a 6-m walk ($P < .001$), both in favor of the exercise group. Low-intensity exercise participation, measured by accelerometry, increased from 341.7 ± 143.3 min/wk to 356.7 ± 112.6 min/wk in the intervention group ($P = .003$). There were no significant postintervention between-group differences were observed for fatigue, QoL, or psychological distress. In a second study by this author (n = 20), a 3-month supervised resistance exercise intervention identical to that described in the previous study, was followed by a 6-month follow up assessment. Gains in ambulation ($P = .046$) and increases in weekly minutes of resistance exercise ($P = .003$) and whole body lean mass ($P = .039$) were maintained at follow-up [66].

Using a different approach, Rief et al [101] examined the effect of isometric resistance exercise training of the paravertebral muscles compared with breathing exercises in a group of patients with spinal bone metastases receiving radiotherapy (n = 60). The intervention involved 30 minutes of exercises that were performed on each day of radiotherapy treatment over a 2-week period and continued 3 times a week for 6 months. Pain scores had reduced from 48 of 100 at baseline to 16 of 100 postintervention in the intervention arm compared with no change (51/100 to 50/100) in the control group ($P < .001$) [102]. There were no differences in fracture rate between groups after either 3 ($P = .59$) or 6 months ($P = .60$) and no difference in overall survival or progression-free survival between the 2 study arms [103]. In addition, pyridinoline and beta-isomer of carboxy-terminal telopeptide of type I collagen, biomarkers of bone turnover, decreased significantly in the resistance arm in comparison to the control group. These biomarkers may be used as a complementary tool for predicting local response to treatment, and for avoiding SRE [104].

Aerobic Versus Resistance Exercise

One randomized trial assigned 66 patients with metastatic cancer, including patients with bone metastases, to a program of either individualized resistance (n = 34) or aerobic exercise (n = 32) [78]. Resistance exercise was completed twice weekly on a circuit of weight training equipment, while aerobic training was completed twice weekly for 30-60 minutes on >1 machine (eg, bike, treadmill). At 10 weeks there were significant improvements in Short Physical Performance Battery total score ($P < .001$), gait speed ($P = .001$), and fatigue ($P = .05$) in both groups. In relation to Short Physical Performance Battery scores, regardless of group assignment, gait ($P = .002$) and chair stand ($P < .001$) subscores improved significantly over time; however, balance subscores did not change in either group. Neither resistance nor aerobic training aggravated fatigue or pain. There was no differential effect of one mode of exercise compared with the other.

Aerobic and Resistance Exercise

Five studies examined the effects of multimodal interventions prescribing both aerobic and resistance programs to patients with metastatic bone disease. A recent randomized controlled trial examined the effects of a multimodal exercise program of resistance, aerobic, and flexibility exercise on physical function in patients (n = 57) with metastatic prostate cancer. This

Table 4
Guide for prescribing exercise for patients with bone metastases (Galvao et al)

	Exercise Mode					
	Resistance			Aerobic		Flexibility
Metastasis Site	Upper	Trunk	Lower	WB	NWB	Static
Pelvis	√	√	√*		√	√
Axial skeleton (lumbar)	√		√		√	√†
Axial skeleton (thoracic/ribs)	√‡		√	√	√	√†
Proximal femur	√	√	√*		√	√
All regions	√‡		√*		√	√†

WB = weight-bearing (eg, walking); NWB = non–weight-bearing (eg, cycling); √ = target exercise region.
* Exclusion of hip extension/flexion – inclusion of knee extension/flexion.
† Exclusion of spine flexion/extension/rotation.
‡ Exclusion of shoulder flexion/extension/abduction/adduction – inclusion of elbow flexion/extension.

was the only study in the current review to prescribe flexibility exercise, advising static stretches to all patients regardless of site of metastases; however, spinal flexion/extension/rotation stretches were excluded in patients with axial or widespread metastases. The exercise intervention, undertaken 3 times per week, resulted in self-reported improvements in physical function ($P = .028$), and objectively measured lower body muscle strength ($P = .033$) with no skeletal complications or increased bone pain [105]. The largest program reviewed (n = 231), randomized patients to an 8-week aerobic and resistance circuit training program or to a usual-care control group. Clinically and statistically significant between-group effects were found in shuttle walk test scores (mean difference of 60 m [95% CI 16.0-103.4 m; $P = .008$]) and hand grip strength scores (mean difference of 2.0 kg [95% CI 0.4-3.5]) in favor of the exercise group postintervention. However, no significant between group effects in the primary outcome, fatigue were reported [22].

In contrast, a single-arm feasibility study of a lifestyle intervention for sedentary men with advanced cancer receiving ADT found significant within-group improvements in fatigue (Functional Assessment of Cancer Therapy: Fatigue) scores ($P < .001$) at 12 weeks. Participants completed 30 minutes of supervised resistance and aerobic exercise twice weekly for the initial 6 weeks and then once weekly for the following 6 weeks. Improvements were maintained at a 6-month follow-up assessment (mean difference: 3.9 points [95% CI 1.1-6.8]; adjusted $P = .007$) [106,107]. Similarly, when the intervention was tested as an RCT, the intervention arm experienced clinically important improvements in Functional Assessment of Cancer Therapy: Fatigue scores at 12 weeks compared with the control arm (mean difference: 5.3 points; 95% CI 2.7-7.9; adjusted $P < .001$). Changes were maintained after withdrawal of supervision at 6 months (mean difference: 3.9 points; 95% CI 1.1-6.8; adjusted $P = .007$). However, clinically important improvements in disease-specific QoL at 3 months (adjusted mean difference: 8.9 points; CI 3.7-14.2) were not sustained after the cessation of the supervised period (adjusted mean difference: 3.3 points; 95% CI 2.6-9.3).

Studies in Animals

Jones et al [108] investigated the effects of exercise on cancer progression and mechanisms of metastasis in an orthotopic model of murine prostate cancer. Mice were randomly assigned to exercise group who completed voluntary wheel-running (n = 28) or a nonintervention control (n = 31) groups. Median running distance ranged from ~4 to ~6 km/d. The primary tumor growth rate, measured by the modulation of circulating host levels of metabolic and sex-steroid hormone levels, improvements in immune surveillance, and reduced systemic inflammation and oxidative damage, was comparable between the exercise and control group across the entire course of the experiment, demonstrating that exercise did not inhibit primary cancer progression. However, exercise did favorably alter genes responsible for metastatic dissemination in the primary tumor, with a shift toward reduced metastasis.

A second study used an in vivo model to investigate the role of skeletal mechanical stimuli on the development and osteolytic capability of secondary breast tumors. For loading, the left limbs of mice were subjected to dynamic compressive loading for 2 or 6 weeks using an established protocol (1200 cycles at 4 Hz, 5 d/wk); nonloaded control mice only underwent anesthesia. Mechanical loading was found to inhibit the growth and osteolytic capability of secondary breast tumors [109]. There may also be an application of the findings of this study in human populations.

Discussion

Studies prescribing exercise for patients living with metastatic cancer report high levels of patient tolerance, acceptability, and adherence. Importantly, no adverse events related to exercise interventions were reported among any of the interventions reviewed. Statistically significant and clinically meaningful improvements in exercise behavior, muscle strength, aerobic fitness,

walking speed, and muscle mass were observed with several different exercise training modalities. Importantly, these benefits occurred without aggravating symptoms such as fatigue and bone pain. However, study quality varied, particularly in relation to study design, and therefore further work validating the reported results is required. Physical exercise programs tailored to the individual patient appear safe, efficacious, and feasible in this population. This review has identified key factors that should be considered when prescribing exercise to patients living with bone metastases.

Patient Assessment and Eligibility

In addition to the standard pre-exercise review of past medical history and physical examination of cardiac, pulmonary, neurologic, and musculoskeletal health [110], a pain assessment should be included for patients with bone metastases, including pain interference with function that may be measured using the BPI. Fracture risk is a key consideration. Studies reviewed reporting adverse events did not find a high fracture incidence with exercise in comparison with control participants, or an association between exercise and fracture risk. However, fracture risk assessments would allow greater risk stratification for this patient group and may allay the fears of health professionals regarding exercise prescription. Tools such as Mirels' Classification Score or the FRAX calculator may prove useful for determining suitability to exercise; however, as established in the exercise interventions reviewed, such tools are rarely used to guide patient eligibility for exercise interventions. Instead, performance scales or predictions of survival length are commonly used to determine participant eligibility, which may unfortunately exclude patients who can exercise safely and stand to gain from increasing activity levels. A number of trials considered for inclusion in this review listed evidence of bone metastases in the hip or spine [43,111-113], or evidence of bone metastases in the spine alone [114], brain, or bone metastases [115,116] as participant exclusion criteria, however, included others with stage IV cancers. The inclusion of patients with bone metastases in exercise studies would have greatly increased the generalizability of results to all patients at this stage of disease. In addition, a number of exercise trials in advanced cancer did not specify whether patients with metastatic bone disease were included [117-119] or specify the site of metastases [120]. Further detail regarding patients' disease status would enable clinicians to ascertain the applicability of study results to specific patient populations in practice.

Exercise Prescription and Instruction

Papers reviewed describe a number of approaches to exercise prescription. The need to individualize exercise prescription and adapt exercises to patient ability were reinforced in all papers reviewed. The heterogeneity of patients presenting with bone metastases means that exercise prescription will vary widely according to the patient's presentation. Some patients present late in the course of their metastatic disease, after failing all treatment modalities, whereas others present without a known primary diagnosis. The purpose of exercise prescription or the desired outcomes will inform the program prescribed. Compromised bone health further complicates exercise prescription. For patients living with metastatic prostate cancer, autoregulation has been introduced as a novel concept. This allows patients to self-determine their capabilities at each session collaboratively with the supervising exercise specialist [121]. It is clear therefore that individualized exercise prescription is required when treating patients with bone metastases to manage unique patient presentations and multifaceted issues.

From the exercise interventions reviewed, different approaches to exercise individualization are described. The most prescriptive approach outlines a systematic method of prescribing resistance exercise based on the location of bone metastases to ensure affected regions are not targeted and mechanical force at areas of metastases is minimized (Table 4) [11,122]. This approach has considerable potential to be used to guide exercise programs that include resistance, aerobics, and flexibility exercises in the clinical setting. This may be of particular importance for patients with more than one bone metastasis, as the system provides guidance for limiting loads to multiple areas of the body.

In addition, circuit exercise classes tailored to individuals and exercise program determined by baseline functional ability have also been prescribed with no exercise-related adverse events [22,78]. This emphasizes the importance clinical reasoning to inform exercise adaptation suitable for metastatic bone disease.

Detailed exercise instructions were described in many studies, such as providing tuition on correct exercise techniques, monitoring effective techniques, and providing guidance on exercise intensity by monitoring heart rate and perceived exertion [10,106,118]. Litterini et al [78] advised numerous safety precautions to accommodate patients' medical history, comorbidities, treatment-related side effects, venous access devices, peripheral neuropathy, pathologic fracture risk, immunosuppression, lymphedema risk, and/or cardiopulmonary issues. For example, participants who had pain with lower extremity weight bearing or who had compromised spinal integrity exercised by walking in a lap pool. This also emphasizes the role of clinical exercise specialists such as physiotherapists. Given the expertise required to ensure safe exercise practice in this cohort, large-scale exercise interventions, eg, community exercise referral schemes, may have a limited role in this population. From the studies reviewed, it appears essential that exercise prescription and supervision be managed by

physiatrists and therapists trained in cancer rehabilitation who are able to complete complex assessments and evaluations of patient response to exercise. In the absence of consensus guidelines, these specialists may be best placed to apply research knowledge into clinical practice and individually tailor exercise for this complex cohort.

Future Areas for Exploration

Exercise may have a role in improving the bone health of patients with metastatic cancer. Where previously exercise was assumed to increase risk of fracture, there is the possibility and transference that undertaking individual prescribed exercise could lower fracture risk in patients. Interventions in the current review describe improvements in bone mineral content and bone turnover markers with both aerobic and resistance exercise training [100,104]. In addition, studies in animals suggest that the mechanical loading of bone involved with exercise may inhibit osteolytic capability and formation of metastatic tumors. Findings indicate the exciting possibility of prescribing exercise to attenuate the progression of bone metastatic disease [109]. There is a need to look at bone turnover markers and radiologic imaging in subsequent studies involving human participants with bone metastases in order obtain a greater understanding of skeletal adaptions to exercise in this population.

Future trials involving larger sample sizes of patients living with bone metastases are planned to expand these preliminary findings of feasibility studies included in this review [122]. A study protocol for a randomized pilot trial involving differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastases under concomitant radiotherapy is currently ongoing. The planned trial aims to show that strengthening of the paravertebral musculature does not only have positive effects on the perception of pain, but may also improve QoL and fatigue in patients with unstable spinal metastases [123]. A protocol for another trial exploring resistance exercise and the suppression of tumor growth in patients with advanced prostate cancer with sclerotic bone metastases has also been published [124]. This study will further enhance knowledge surrounding the effect of exercise on systemic markers of metastases. The forthcoming INTERVAL Trial (INTense Exercise foR surVivAL Among Men With Metastatic Castrate-Resistant Prostate Cancer), part of the Movember Global Prostate Cancer, Exercise and Metabolic Health Initiative, will also contribute much knowledge in the area of exercise and metastatic disease [32]. This initiative will involve a global multicenter exercise trial for men with advanced cancer looking at overall survival as the primary endpoint. Additional endpoints will include measures of strength, physical function, and physical activity and will focus on the mechanisms of action underpinning the relationship between physical activity and the biology of advanced disease. The current paper did not examine the role of exercise for children with bone metastasis or the unique challenges of bone metastases in growing bone. This is an area that would benefit from attention in future reviews.

Conclusion

Exercise interventions for patients with bone metastases are associated with positive physical and self-reported outcomes and a low rate of adverse events. Exercise prescription to patients with bone metastases does involve complex decision-making; however, a number of tools are available that may inform both the assessment of patients and the prescription of exercise.

Uncited Reference

68.

References

1. Weinstein JN. Differential diagnosis and surgical treatment of pathologic spine fractures. Instructional Course Lectures 1992;41:301-315.
2. Conte P, Coleman R. Bisphosphonates in the treatment of skeletal metastases. Semin Oncol 2004;31:59-63.
3. Zore Z, Zore IF, Matejčić A, Kamal M, Arslani N, Zlatarić DK. Surgical treatment of pathologic fractures in patients with metastatic tumors. Coll Antropol 2009;33:1383-1386.
4. Lipton A, Uzzo R, Amato RJ, et al. The science and practice of bone health in oncology: Managing bone loss and metastasis in patients with solid tumors. J Natl Compr Cancer Netw 2009;7(Suppl 7):S1-S29; quiz S30.
5. Jasmin C, Coleman RE, Coia LR, Capanna R, Saillant G, eds. Textbook of Bone Metastases. Hoboken, NJ: John Wiley and Sons; 2005.
6. Santiago-Palma J, Payne R. Palliative care and rehabilitation. Cancer 2001;92:1049-1052.
7. Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, Harris SR. Effects of exercise intervention on persons with metastatic cancer: A systematic review. Physiother Can 2009;61:141-153.
8. Salakari MR, Surakka T, Nurminen R, Pylkkanen L. Effects of rehabilitation among patients with advances cancer: A systematic review. Acta Oncol 2015;54:618-628.
9. ~~Office of Disease Prevention and Health Promotion. Physical Activity Guidelines for Americans. Available at https://health.gov/paguidelines/guidelines/. Accessed XXX [Internet 2008].~~
10. Porock D, Kristjanson LJ, Tinnelly K, Duke T, Blight J. An exercise intervention for advanced cancer patients experiencing fatigue: A pilot study. J Palliat Care 2000;16:30-36.
11. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis 2013;16:328-335.
12. Sheill G, Guinan E, Hevey D, Neill LO, Hussey J. Physical activity and metastatic disease: The views of physiotherapists in Ireland. Physiotherapy 2016;102:e134.
13. Sheill G, Guinan E, Neill LO, Hevey D, Hussey J. Physical activity and advanced cancer: The views of oncology and palliative care physicians in Ireland. Irish J Med Sci, in press.
14. Saad F. Bone-targeted therapy in prostate cancer. Eur J Cancer Suppl 2013;11:257-259.

15. Lowe SS, Watanabe SM, Baracos VE, Courneya KS. Physical activity interests and preferences in palliative cancer patients. Support Care Cancer 2010;18:1469-1475.
16. Zopf EM, Newton RU, Taaffe DR, et al. Associations between aerobic exercise levels and physical and mental health outcomes in men with bone metastatic prostate cancer: A cross-sectional investigation. Eur J Cancer Care (Engl), in press.
17. Klassen O, Schmidt ME, Ulrich CM, et al. Muscle strength in breast cancer patients receiving different treatment regimes. J Cachexia Sarcopenia Muscle 2017;8:305-316.
18. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: A comprehensive cross-sectional investigation. Prostate Cancer Prostatic Dis 2009;12:198-203.
19. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920-2926.
20. Trosclair D, Bellar D, Judge LW, Smith J, Mazerat N, Brignac A. Hand-Grip Strength as a Predictor of Muscular Strength and Endurance. J Strength Cond Res 2011;25:599.
21. Massy-Westropp NM, Gill TK, Taylor AW, Bohannon RW, Hill CL. Hand Grip Strength: Age and gender stratified normative data in a population-based study. BMC Res Notes 2011;4:127.
22. Oldervoll LM, Loge JH, Lydersen S, et al. Physical exercise for cancer patients with advanced disease: A randomized controlled trial. Oncologist 2011;16:1649-1657.
23. Yee J, Davis GM, Beith JM, et al. Physical activity and fitness in women with metastatic breast cancer. J Cancer Surviv 2014;8:647-656.
24. Dudzińska-Griszek J, Szuster K, Szewieczek J. Grip strength as a frailty diagnostic component in geriatric inpatients. Clin Interv Aging 2017;12:1151-1157.
25. Millor N, Lecumberri P, Gomez M, Martinez-Ramirez A, Izquierdo M. An evaluation of the 30-s chair stand test in older adults: Frailty detection based on kinematic parameters from a single inertial unit. J Neuroeng Rehabil 2013;10:86.
26. Rief H, Omlor G, Akbar M, et al. Feasibility of isometric spinal muscle training in patients with bone metastases under radiation therapy—first results of a randomized pilot trial. BMC Cancer 2014;14:67.
27. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999;70:113-119.
28. Garber CE, Greaney ML, Riebe D, Nigg CR, Burbank PA, Clark PG. Physical and mental health-related correlates of physical function in community dwelling older adults: A cross sectional study. BMC Geriatr 2010;10:6.
29. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. Br J Cancer 2015;112:194-198.
30. Reiman MP, Manske RC. The assessment of function: How is it measured? A clinical perspective. J Man Manip Ther 2011;19:91-99.
31. Latham NK, Mehta V, Nguyen AM, et al. Performance-based or self-report measures of physical function: Which should be used in clinical trials of hip fracture patients? Arch Phys Med Rehabil 2008;89:2146-2155.
32. Janssen SJ, Paulino Pereira NR, Raskin KA, et al. A comparison of questionnaires for assessing physical function in patients with lower extremity bone metastases. J Surg Oncol 2016;114:691-696.
33. Jensen RE, Potosky AL, Reeve BB, et al. Validation of the PROMIS physical function measures in a diverse US population-based cohort of cancer patients. Qual Life Res 2015;24:2333-2344.
34. Jones LW, Hornsby WE, Goetzinger A, et al. Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. Lung Cancer 2012;76:248-252.
35. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. Public Health Rep 1985;100:126-131.
36. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. J Cancer Surviv 2010;4:87-100.
37. Ferriolli E, Skipworth RJE, Hendry P, et al. Physical activity monitoring: A responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? J Pain Symptom Manage 2012;43:1025-1035.
38. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409-1426.
39. Drake MT. Osteoporosis and cancer. Curr Osteoporos Rep 2013;11:163-170.
40. Hussain SA, Weston R, Stephenson RN, George E, Parr NJ. Immediate dual energy X-ray absorptiometry reveals a high incidence of osteoporosis in patients with advanced prostate cancer before hormonal manipulation. BJU Int 2003;92:690-694.
41. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 2004;15:1003-1008.
42. Wooldridge JE, Anderson CM, Perry MC. Corticosteroids in advanced cancer. Oncology (Williston Park) 2001;15:225-234; discussion 34-6.
43. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. Med Sci Sports Exerc 2014;46:1482-1488.
44. Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Cancer Netw 2010;8:162-200.
45. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int 1997;7:390-406.
46. Rief H, Forster R, Rieken S, et al. The influence of orthopedic corsets on the incidence of pathological fractures in patients with spinal bone metastases after radiotherapy. BMC Cancer 2015;15:745.
47. Cosman F, De Beur S, LeBoff M, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359-2381.
48. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. American College of Sports M. American College of Sports Medicine Position Stand: Physical activity and bone health. Med Sci Sports Exerc 2004;36:1985-1996.
49. Sonmez M, Akagun T, Topbas M, et al. Effect of pathologic fractures on survival in multiple myeloma patients: A case control study. J Exp Clin Cancer Res 2008;27:11.
50. Saad F, Lipton A, Cook R, Chen Y-M, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer 2007;110:1860-1867.
51. Bunting R, Lamont-Havers W, Schweon D, Kliman A. Pathologic fracture risk in rehabilitation of patients with bony metastases. Clin Orthop Rel Res 1985:222-227.
52. Bunting RW, Boublik M, Blevins FT, Dame CC, Ford LA, Lavine LS. Functional outcome of pathologic fracture secondary to malignant disease in a rehabilitation hospital. Cancer 1992;69:98-102.
53. Jawad MU, Scully SP. In Brief: Classifications in Brief: Mirels' classification: Metastatic disease in long bones and impending pathologic fracture. Clin Orthop Rel Res 2010;468:2825-2827.
54. Smith L, McCourt O, Henrich M, et al. Multiple myeloma and physical activity: A scoping review. BMJ Open 2015;5:e009576.
55. Gulia A, Byregowda S, Panda P. Palliative care in musculoskeletal oncology. Indian J Palliat Care 2016;22:244-251.
56. Adler RA. Management of osteoporosis in men on androgen deprivation therapy. Maturitas 2011;68:143-147.

57. Saylor PJ, Kaufman DS, Michaelson MD, Lee RJ, Smith MR. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer. J Urol 2010; 183:2200-2205.
58. Goodheart JR, Cleary RJ, Damron TA, Mann KA. Simulating activities of daily living with finite element analysis improves fracture prediction for patients with metastatic femoral lesions. J Orthop Res 2015;33:1226-1234.
59. Damron TA, Nazarian A, Entezari V, et al. CT-based structural rigidity analysis is more accurate than Mirels' scoring for fracture prediction in metastatic femoral lesions. Clin Orthop Rel Res 2016;474:643-651.
60. Sabino MA, Mantyh PW. Pathophysiology of bone cancer pain. J Support Oncol 2005;3:15-24.
61. Laird BJ, Walley J, Murray GD, Clausen E, Colvin LA, Fallon MT. Characterization of cancer-induced bone pain: An exploratory study. Supportive Care Cancer 2011;19:1393-1401.
62. Ghosh A, Berger A. Opioids, adjuvants, and interventional options for pain management of symptomatic metastases. Ann Palliat Med 2014;3:172-191.
63. Chow E, James J, Barsevick A, et al. Functional interference clusters in cancer patients with bone metastases: A secondary analysis of RTOG 9714. Int J Radiat Oncol Biol Phys 2010;76:1507-1511.
64. Wu JS, Beaton D, Smith PM, Hagen NA. Patterns of pain and interference in patients with painful bone metastases: A brief pain inventory validation study. J Pain Symptom Manage 2010;39: 230-240.
65. Fidler M. Incidence of fracture through metastases in long bones. Acta Orthop Scand 1981;52:623.
66. Cormie P, Galvao DA, Spry N, Joseph D, Taaffe DR, Newton RU. Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: Longitudinal results of a pilot study. Supportive Care Cancer 2014; 22:1537-1548.
67. National Institute for Health and Care Excellence. Metastatic spinal cord compression in adults: Risk assessment, diagnosis and management. Clinical Guideline 75 2008. Available at https://www.nice.org.uk/guidance/cg75. Accessed XXX.
68. Guidelines and Audit Implementation Network. Guidelines for the Rehabilitation of Patients with Metastatic Spinal Cord Compression (MSCC). Assessment and Care Provision by Occupational Therapists and Physiotherapists in the Acute Sector January 2014. Available at https://www.rqia.org.uk/RQIA/files/cb/cba33182-deab-46ae-acd1-d27279d9847c.pdf. Accessed XXX.
69. Bunting RW, Shea B. Bone metastasis and rehabilitation. Cancer 2001;92:1020-1028.
70. Riccio AI, Wodajo FM, Malawer M. Metastatic carcinoma of the long bones. Am Fam Physician 2007;76:1489-1494.
71. Yang L, Du S. Efficacy and safety of zoledronic acid and pamidronate disodium in the treatment of malignant skeletal metastasis: A meta-analysis. Medicine 2015;94:e1822.
72. Petcu EB, Schug SA, Smith H. Clinical evaluation of onset of analgesia using intravenous pamidronate in metastatic bone pain. J Pain Symptom Manage 2002;24:281-284.
73. Smith HS, Mohsin I. Painful boney metastases. Korean J Pain 2013; 26:223-241.
74. Lutz S, Lo SS, Chow E, Sahgal A, Hoskin P. Radiotherapy for metastatic bone disease: Current standards and future prospectus. Exp Rev Anticancer Ther 2010;10:683-695.
75. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: Final results of the Study by the Radiation Therapy Oncology Group. Cancer 1982;50:893-899.
76. Wu JSY, Monk G, Clark T, Robinson J, Eigl BJC, Hagen N. Palliative radiotherapy improves pain and reduces functional interference in patients with painful bone metastases: A quality assurance study. Clin Oncol 2006;18:539-544.
77. Zeng L, Chow E, Zhang LY, et al. Comparison of pain response and functional interference outcomes between spinal and non-spinal bone metastases treated with palliative radiotherapy. Supportive Care Cancer 2012;20:633-639.
78. Litterini AJ, Fieler VK, Cavanaugh JT, Lee JQ. Differential effects of cardiovascular and resistance exercise on functional mobility in individuals with advanced cancer: A randomized trial. Arch Phys Med Rehabil 2013;94:2329-2335.
79. Rief H, Akbar M, Keller M, et al. Quality of life and fatigue of patients with spinal bone metastases under combined treatment with resistance training and radiation therapy—a randomized pilot trial. Radiat Oncol 2014;9:151.
80. Stefani L, Galanti G, Klika R. Clinical Implementation of Exercise Guidelines for Cancer Patients: Adaptation of ACSM's Guidelines to the Italian Model. J Functional Morphol Kinesiol 2017;2:4.
81. Zore Z, Filipovic Zore I, Matejcic A, Kamal M, Arslani N, Knezovic Zlataric D. Surgical treatment of pathologic fractures in patients with metastatic tumors. Coll Antropol 2009;33:1383-1386.
82. Saliou G, Kocheida el M, Lehmann P, et al. Percutaneous vertebroplasty for pain management in malignant fractures of the spine with epidural involvement. Radiology 2010;254:882-890.
83. Qian Z, Sun Z, Yang H, Gu Y, Chen K, Wu G. Kyphoplasty for the treatment of malignant vertebral compression fractures caused by metastases. J Clin Neurosci 2011;18:763-767.
84. Gokaslan ZL, York JE, Walsh GL, et al. Transthoracic vertebrectomy for metastatic spinal tumors. J Neurosurg 1998;89: 599-609.
85. Carlin L, Sibley K, Jenkinson R, et al. Exploring Canadian surgeons' decisions about postoperative weight bearing for their hip fracture patients. J Eval Clin Pract, in press.
86. Hortobagyi GN. Commentary: Role of bone-modifying agents in metastatic breast cancer. J Oncol Practice 2011;7:121-123.
87. Serpa Neto A, Tobias-Machado M, Esteves MA, et al. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: A systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2012;15:36-44.
88. National Institute for Health and Care Excellence. Metastatic spinal cord compression in adults: Risk assessment, diagnosis and management. Clinical Guideline 75 2008. Available at https://www.nice.org.uk/guidance/cg75. Accessed XXX.
89. Hayes DF. Patient education: Treatment of metastatic breast cancer (Beyond the Basics). UpToDate2016. Available at https://www.uptodate.com/contents/treatment-of-metastatic-breast-cancer-beyond-the-basics. Accessed XXX.
90. Narayanan P. Denosumab: A comprehensive review. South Asian J Cancer 2013;2:272-277.
91. Portenoy RK. Treatment of cancer pain. Lancet 2011;377:2236-2247.
92. Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. Drug Saf 1999; 21:389-406.
93. Coleman RE. Bisphosphonates in breast cancer. Ann Oncol 2005; 16:687-695.
94. Ralston SH. Medical management of hypercalcaemia. Br J Clin Pharmacol 1992;34:11-20.
95. Mirrakhimov AE. Hypercalcemia of malignancy: An Update on pathogenesis and management. North Am J Med Sci 2015;7: 483-493.
96. Swenson KK, Nissen MJ, Anderson E, Shapiro A, Schousboe J, Leach J. Effects of exercise vs bisphosphonates on bone mineral density in breast cancer patients receiving chemotherapy. J Support Oncol 2009;7:101-107.
97. Angelis KD, Rodrigues B, Zanesco A, et al. The importance of animal studies in exercise science. Motriz: Revista de Educação Física 2017;23:e101625.
98. Ligibel JA, Giobbie-Hurder A, Shockro L, et al. Randomized trial of a physical activity intervention in women with metastatic breast cancer. Cancer 2016;122:1169-1177.
99. Uth J, Hornstrup T, Christensen JF, et al. Efficacy of recreational football on bone health, body composition, and physical

functioning in men with prostate cancer undergoing androgen deprivation therapy: 32-week follow-up of the FC prostate randomised controlled trial. Osteoporos Int 2016;27:1507-1518.
100. Uth J, Hornstrup T, Christensen JF, et al. Football training in men with prostate cancer undergoing androgen deprivation therapy: Activity profile and short-term skeletal and postural balance adaptations. Eur J Appl Physiol 2016;116:471-480.
101. Rief H, Petersen LC, Omlor G, et al. The effect of resistance training during radiotherapy on spinal bone metastases in cancer patients—A randomized trial. Radiother Oncol 2014;112:133-139.
102. Rief H, Welzel T, Omlor G, et al. Pain response of resistance training of the paravertebral musculature under radiotherapy in patients with spinal bone metastases—a randomized trial. BMC Cancer 2014;14.
103. Rief H, Bruckner T, Schlampp I, et al. Resistance training concomitant to radiotherapy of spinal bone metastases—survival and prognostic factors of a randomized trial. Radiation Oncology 2016;11:97.
104. Rief H, Omlor G, Akbar M, et al. Biochemical markers of bone turnover in patients with spinal metastases after resistance training under radiotherapy—a randomized trial. BMC Cancer 2016;16:231.
105. Galvao DA, Taaffe DR, Spry N, et al. Exercise preserves physical function in prostate cancer patients with bone metastases. Med Sci Sports Exerc 2018;50:393-399.
106. Bourke L, Doll H, Crank H, Daley A, Rosario D, Saxton JM. Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. Cancer Epidemiol Biomarkers Prev 2011;20:647-657.
107. Bourke L, Gilbert S, Hooper R, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: A randomised controlled trial. Eur Urol 2014;65:865-872.
108. Jones LW, Antonelli J, Masko EM, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. J Appl Physiol (1985) 2012;113:263-272.
109. Lynch ME, Brooks D, Mohanan S, et al. In vivo tibial compression decreases osteolysis and tumor formation in a human metastatic breast cancer model. J Bone Miner Res 2013;28:2357-2367.
110. Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol 2010;11:914-916.
111. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol 2010;28:340-347.
112. Stevinson C, Fox KR. Feasibility of an exercise rehabilitation programme for cancer patients. Eur J Cancer Care (Engl) 2006;15:386-396.
113. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 2003;21:1653-1659.
114. Kuehr L, Wiskemann J, Abel U, Ulrich CM, Hummler S, Thomas M. Exercise in patients with non-small cell lung cancer. Med Sci Sports Exerc 2014;46:656-663.
115. Quist M, Rorth M, Langer S, et al. Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: A pilot study. Lung Cancer 2012;75:203-208.
116. Quist M, Adamsen L, Rorth M, Laursen JH, Christensen KB, Langer SW. The impact of a multidimensional exercise intervention on physical and functional capacity, anxiety, and depression in patients with advanced-stage lung cancer undergoing chemotherapy. Integr Cancer Ther 2015;14:341-349.
117. Cheville AL, Girardi J, Clark MM, et al. Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well-being. Am J Phys Med Rehabil 2010;89:611-619.
118. Oldervoll LM, Loge JH, Paltiel H, et al. The effect of a physical exercise program in palliative care: A Phase II study. J Pain Symptom Manage 2006;31:421-430.
119. Rummans TA, Clark MM, Sloan JA, et al. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: A randomized controlled trial. J Clin Oncol 2006;24:635-642.
120. Carson JW, Carson KM, Porter LS, Keefe FJ, Shaw H, Miller JM. Yoga for women with metastatic breast cancer: results from a pilot study. J Pain Symptom Manage 2007;33:331-341.
121. Hart NH, Galvão DA, Newton RU. Exercise medicine for advanced prostate cancer. Curr Opin Support Palliat Care 2017;11:247-257.
122. Galvão DA, Taaffe DR, Cormie P, et al. Efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases: A randomized controlled trial. BMC Cancer 2011;11:517.
123. Welte SE, Wiskemann J, Scharhag-Rosenberger F, et al. Differentiated resistance training of the paravertebral muscles in patients with unstable spinal bone metastasis under concomitant radiotherapy: Study protocol for a randomized pilot trial. Trials 2017;18:155.
124. Hart NH, Newton RU, Spry NA, et al. Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy. BMJ Open 2017;7:e014458.

Disclosure

G.S. Discipline of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin 8, Ireland. Address correspondence to: G.S.; e-mail: sheilg@tcd.ie
Disclosures related to this publication: grant, World Cancer Research Fund (money to institution).

E.M.G. School of Medicine, Trinity College Dublin, Dublin, Ireland
Disclosure: nothing to disclose

N.P. Physiotherapy Department, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
Disclosure: nothing to disclose

J.H. Discipline of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin, Ireland
Disclosure: nothing to disclose

A researcher on this paper (G.S.) was supported by funding attained through the World Cancer Research Fund (WCRF: 2013/1003, TCD: Award 12799 Project 202370).

Submitted for publication November 22, 2017; accepted February 13, 2018.

Health Research Authority

NRES Committee London - Camden & Islington

Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne & Wear
NE32 3DT

Telephone: 0191 4283545

10 December 2014

Dr Mieke Van Hemelrijck
Lecturer in Cancer Epidemiology
Kings College London
Research Oncology, Bermondsey Wing 3rd floor
Guy's Hospital
Great Maze Pond
SE1 9RT

Dear Dr Van Hemelrijck

Study title: The ExPeCT Trial (Exercise, Prostate cancer and Circulating Tumour cells): Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behaviour in obese men with prostate cancer
REC reference: 14/LO/1859
IRAS project ID: 146754

Thank you for your e-mail correspondence of 8th and 9th December 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Hayley Henderson, nrescommittee.london-camdenandislington@nhs.net. Under very limited circumstances (e.g. for

student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	Expires 31/07/2015	01 August 2014
GP/consultant information sheets or letters [GP Letter]	V.1	01 June 2014
Other [Exercise Diary]	1, October 2014	
Participant consent form	2.0, November 2014	
Participant information sheet (PIS)	2.0, November 2014	
REC Application Form [REC_Form_03102014]		03 October 2014
Research protocol or project proposal	2.0, November 2014	
Response to Request for Further Information		07 December 2014
Summary CV for Chief Investigator (CI) [C.I. CV]		
Validated questionnaire	3.0, November 2014	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/1859	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp H Hendra

Mrs Rosie Glazebrook

Chair

Email:nrescommittee.london-camdenandislington@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Ms Barbara Dahill, King's College London

Mrs Karen Ignatian, Guy's and St Thomas' Foundation NHS Trust

Mater Misericordiae University Hospital
Sisters of Mercy
Eccles Street, Dublin 7, Ireland

Ospidéal Ollscoile Mater Misericordiae
Siúracha na Trócaire
Sráid Eccles, Baile Átha Cliath 7, Éire

Tel: +353 1 8032000 Fax: +353 1 8032404 Email: mmh@mater.ie Web: www.mater.ie

Not for prescription purposes

Professor John McCaffrey
Consultant Medical Oncologist
Mater Misericordiae University Hospital
Eccles Street
Dublin 7

RECEIVED 29 JAN 2016

15th January 2016

Our Ref: 1/378/1760

RE: Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behaviour in obese men with prostate cancer – The ExPeCT Study
Exercise, Prostate cancer and Circulating Tumour cells
ICORG 15-21
Protocol, Version 1.4 14th September 2015
Patient Information Leaflet, ICORG Version 1.0 10-Aug-2015, MMUH Version 2.0 03-Nov-2015
Informed Consent Form, ICORG Version 1.0 10-Aug-2015, MMUH Version 2.0 03-Nov-2015
Patient Information Leaflet, ICORG Version 1.0 10-Aug-2015, MPH Version 2.0 03-Nov-2015
Informed Consent Form, ICORG Version 1.0 10-Aug-2015, MPH Version 2.0 03-Nov-2015

Dear Prof McCaffrey

I acknowledge receipt of your correspondence dated 3rd November 2015 enclosing a revised Patient Information Leaflet (ICORG Version 1.0 10-Aug-2015, MMUH and MPH Version 2.0 03-Nov-2015), revised Informed Consent Form (ICORG Version 1.0 10-Aug-2015, MMUH and MPH Version 2.0 03-Nov-2015) and clarifying security arrangements for samples and data for this research study as requested by the Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee) and enclosing an amended Protocol (Version 1.4 14th September 2015) for approval; this research study to be carried out at the Mater Misericordiae University Hospital (MMUH) and Mater Private Hospital (MPH).

This correspondence has been noted. The revised Patient Information Leaflet, revised Informed Consent Form and amended Protocol have been approved. Approval to proceed with this research study at the MMUH and MPH is granted; this approval is valid until 21st October 2017.

It is your responsibility to adhere to the approved study protocol and ensure that all investigators involved with the research only use the approved documents without deviation (unless they have been approved by the Research Ethics Committee), to submit annual reports setting out the progress of the research (giving details of the number of participants who have been recruited, the number who have completed the study and details of any adverse events etc.) and to notify the Research Ethics Committee when the research is concluded.

The Mater Misericordiae University Hospital and Mater Private Hospital Research Ethics Committee would like to remind all investigators involved in research of their legal obligations under the law on Data Protection.

Yours sincerely

Prof Malcolm Kell
Chairman
Research Ethics Committee

c.c. Ms Deirdre Wynne, Business Manager Oncology/Haematology Clinical Trials Research Unit
Ms Aoife Vaughan, tCRA, ICORG
Ms Verena Murphy, Clinical Program Leader, ICORG
Ms Kathryn Holly, Mater Private Hospital

RECEIVED 02 OCT 2015

Beaumont Hospital
Ethics (Medical Research) Committee

25th September 2015

REC reference: 15/73

Protocol: ExPeCT ICORG 15-21

Dr. Verena Murphy
Clinical Program Leader (CPL)
ICORG
60 Fitzwilliam Square North
Dublin 2

Dear Dr. Murphy

RE: 15/73 – Prof. Stephen Finn (SJH) – The ExPeCT Trial (Exercise, Prostate Cancer and Circulating Tumour cells): Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behaviour in obese men with prostate cancer (ICORG 15-21)

Consultant co-investigator: Dr. Liam Grogan

Further to correspondence dated 16th September 2015, I note your important *"commitment to return residual tissue material to Beaumont Hospital immediately."*

Please find enclosed research ethics committee approval for this study to proceed subject to this commitment.

With best regards

Yours sincerely

Dr. Peter Branagan
Convenor
Ethics (Medical Research) Committee

c.c.

Dr. Liam Grogan
Consultant Medical Oncologist
Beaumont Hospital

Ethics (Medical Research) Committee - Beaumont Hospital
Notification of ERC/IRB Approval

Principal Investigator: Prof. Stephen Finn (SJH)

REC reference: 15/73 **Protocol: ExPeCT ICORG 15-21**

Protocol Title: The ExPeCT Trial (Exercise, Prostate Cancer and Circulating Tumour cells): Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behaviour in obese men with prostate cancer (ICORG 15-21)

Ethics Committee Meeting Date: 27th August 2015

Final Approval Date: 25th September 2015

From: Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

Documents Reviewed

Document and Date	Date Reviewed	Approved
Application Form, V1.0, 10/8/15, signed S. Finn, 10/8/15	25/9/15	Yes
Trial Protocol, V1.4, 14/9/15	25/9/15	Yes
Patient Information Leaflet, ICORG V1.0, 10/8/15, BH V2.0,16/9/15	25/9/15	Yes
Informed Consent Form, ICORG V1.0, 10/8/15, BH V2.0,16/9/15	25/9/15	Yes
Cert of Insurance, 087640MMA15A, ICORG	25/9/15	Noted
CV: S. Finn 5/8/15, L. Grogan, 27/1/14	25/9/15	Noted

Dr. Peter Branagan
ERC/IRB Convenor's Signature
Approval # 1, dated 25th September 2015

Condition of Approval: All residual tissue to be returned to Beaumont Hospital immediately

Terms of Approval

- The protocol and research must comply with all relevant Irish legislative requirements and the researchers must abide by the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice.

- Prior approval from the Ethics Committee must be sought for any proposed changes/amendments to this protocol and research.

- Annual Progress Reports and a Final report must be supplied to the Ethics Committee.

ANNUAL REPORT DUE IN SEPTEMBER EACH YEAR (3 YEAR STUDY)

- All relevant information about serious adverse reactions and new events likely to affect the safety of the subjects must be reported to the Ethics (Medical Research) Committee in writing.

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Ms. Aoife Vaughan
ICORG
60 Fitzwilliam Square
Dublin 2

30th October 2015

Re: The ExPeCT Trial (Exercise, prostate cancer and circulating tumour cells): Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behavior in obese men with prostate cancer

REC Reference: 2014-11 List 41 (6)
REC Reference: 2015 List 37 (8) (Please quote reference on all correspondence)

Dear Ms. Vaughan

Thank you for your recent correspondence dated 20th October to SJH/AMNCH Research Ethics Committee in which you requested approval for a non-substantial amendment to the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed and approved your amendment.

The following was reviewed:

- Form 4 – Notification of Amendment form 20 Oct 15
- ExPeCT Protocol Version 1.4 14 Sep 15
- ICORG 15-21 ExPeCT Trial PIL, ICORG Version 1.0 10 Aug 15 STH/AMNCH Version 2.0 20 Oct 2015
- ICORG 15-21 ExPeCT Trial CF, ICORG Version 1.0 10 Aug 15 STH/AMNCH Version 2.0 20 Oct 2015

Yours sincerely

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

Saint Luke's
Radiation Oncology
Network
St Luke's Hospital

Dr. Orla Casey,
Translational Research Co-Ordinator,
Cancer Trials Ireland,
60 Fitzwilliam Square North,
DUBLIN 2.

19th September 2016.

Re: ICORG 15-21. The ExPeCT Trial (Exercise, prostate cancer and circulating tumour cells): Evasion of immune editing by circulating tumour cells is an exercise-modifiable mechanism underlying aggressive behaviour in obese men with prostate cancer.

Dear Dr. Casey,

Your letter dated 5th August 2016 regarding the above referenced research study was reviewed at a meeting of the Research Ethics Committee (REC) held on 8th September 2016.

1. The REC noted that the study exclusion criteria has been amended as per its recommendations of 12th February 2016.

2. Amendments to the Protocol and PIL/CF as detailed in your submission were reviewed and approved. I am pleased to confirm that REC approval is now in place for:

   - Protocol Version 1.5, dated 28-Jul-2016.
   - PIL - Cancer Trials Ireland Version 2.0, dated 05-Aug-2016, SLRON Version 3.0, dated 05-Aug-2016.
   - Consent Form - Cancer Trials Ireland Version 2.0, dated 05-Aug-2016, SLRON Version 2.0, dated 05-Aug-2016.

With kind regards,
Yours sincerely,

pp. _____

Dr. Sheelah Ryan,
Chair, Research Ethics Committee,
St. Luke's Radiation Oncology Network.

c.c. Dr. Moya Cunningham & Ms. Lesley McDonagh, SLRON.

St Luke's Hospital, Oaklands Drive, Highfield Road, Rathgar, Dublin 6.
Ospidéal Naomh Lúcas, Baile Átha Cliath 6.
Telephone: 01 406 5000; Fax: 01 406 5222; Email: radiotherapy.stlukes@slh.ie; www.stlukesnetwork.ie

Appendix 3: Ethical Approval Letter Health Professionals Study

Coláiste na Tríonóide, Baile Átha Cliath
Trinity College Dublin
Ollscoil Átha Cliath | The University of Dublin

Grainne Sheill
Discipline of Physiotherapy
Trinity Centre for Health Sciences
St. James's Hospital
James's Street
Dublin 8

23rd December 2015

Ref: 20150609

Title of Study: The attitudes of health professional towards recommending physical activity to metastatic patients

Dear Ms Sheill,

The School of Medicine Research Ethics Committee has reviewed your amendment request form; we are pleased to inform you that the above amended project has been approved.

Yours sincerely,

Professor Thomas Rogers
Chairperson
School of Medicine Research Ethics Committee

An tOllamh Paul Browne MB, FRCPI, FRCPath
Ceann Scoil an Leighis

Professor Paul Browne MB, FRCPI, FRCPath
Head of School of Medicine

Ms. Orla Bannon
Riarthóir na Scoile

Ms. Orla Bannon
School Administrator

Scoil an Leighis
An Institiúid Eolaíochtaí Bithleighis
Coláiste na Tríonóide, Baile Átha Cliath
Ollscoil Átha Cliath
152-160 Sráid an Phiarsaigh
Baile Átha Cliath 2, Éire.

School of Medicine
Trinity Biomedical Sciences Institute
Trinity College Dublin
The University of Dublin
152-160 Pearse Street
Dublin 2, Ireland.

+353 1 896 1476
medicine@tcd.ie
www.medicine.tcd.ie

Appendix 4: Published Paper: The Views of Patients with Metastatic Prostate Cancer towards Physical Activity: A Qualitative Exploration

Supportive Care in Cancer
https://doi.org/10.1007/s00520-017-4008-x

ORIGINAL ARTICLE

The views of patients with metastatic prostate cancer towards physical activity: a qualitative exploration

G. Sheill[1] · E. Guinan[2] · L. O Neill[1] · D. Hevey[3] · J. Hussey[1]

Received: 2 June 2017 / Accepted: 5 December 2017

Abstract
Purpose Patients with metastatic cancer can experience debilitating symptoms, which may influence attitudes towards and engagement in physical activity. This study aimed to examine the attitudes of patients living with metastatic prostate cancer towards physical activity.
Materials and methods Semi-structured interviews were completed with male patients living with metastatic prostate cancer. Interviews included eight questions related to patients' attitudes towards physical activity. Content analysis was conducted on the transcribed interview data. Twenty men with metastatic prostate cancer (mean age 71 ± 8.5 years; body mass index 30.19 ± 5.37 kg/cm^2) and associated bone metastases (55% with >2 regions affected) participated in the study.
Results Men's views towards physical activity were coded into the following major themes: (1) barriers to physical activity, (2) benefits of physical activity, (3) a reduction in physical activity levels post diagnosis and (4) social support for physical activity. Symptoms of metastatic prostate cancer and treatment side effects including pain and fatigue negatively influenced activity participation. In addition, many generic barriers to physical activity were described such as bad weather and a lack of suitable facilities for exercising in rural areas.
Conclusion Men living with metastatic prostate cancer have unique needs regarding physical activity related to symptoms of both their cancer and cancer treatment. There is a need to increase prompts that encourage those with metastatic prostate cancer to maintain/increase physical activity levels post diagnosis. Given the individualised needs of this patient group, referral to a cancer exercise specialist should be considered for prescription of tailored physical activity programmes.
Trial registration Clinicaltrials.gov NLM Identifier: NCT02453139

Keywords Physical activity · Advanced cancer · Metastases · Qualitative · Exercise

Introduction

An increasing number of patients with metastatic prostate cancer are now receiving life-prolonging treatment [1]. The estimated 5-year survival rate in patients diagnosed with advanced prostate cancer, including metastatic cancer, is now 30–46% [2]. There is a growing body of evidence detailing the many benefits of staying active through all stages of the cancer continuum, including the metastatic stages of disease [2–5]. Individually prescribed physical activity programmes can be safely introduced for patients with many symptoms of advanced disease, including bone metastases [1, 2, 6]. A recent systematic review showed that increasing physical activity levels can improve measures of physical performance and quality of life (QoL) for this patient cohort [7]. Men with metastatic prostate cancer who do not meet aerobic exercise guidelines have also been shown to have significantly lower physical functioning, role functioning (physical and emotional) and general health scores than men who met the guidelines [8]. When patients are not able to undertake vigorous activities, even low-intensity physical activity after a cancer diagnosis is associated with improved outcomes [9, 10].

✉ G. Sheill
sheillg@tcd.ie

[1] Discipline of Physiotherapy, School of Medicine, Trinity College Centre for Health Sciences, James's Street, Dublin 8, Ireland

[2] School of Medicine, Trinity College Centre for Health Sciences, James's Street, Dublin 8, Ireland

[3] School of Psychology, Trinity College Dublin, College Green, Dublin 2, Ireland

Published online: 14 December 2017

Patients with metastatic cancer may experience multiple symptoms such as pain, breathlessness, fatigue and nausea [11], which may limit engagement with physical activity. Despite this, previous research has concluded that >90% of patients with advanced cancer are interested in completing physical activity programmes [12]. However, many patients living with metastases become inactive due to the side effects of cancer and its associated treatments, or the fear of skeletal fracture [13]. A previous study of 55 patients with metastatic prostate cancer demonstrated only 29% of participants met the current aerobic exercise guidelines for cancer survivors while 71% were insufficiently active [8]. It is essential to make exercise interventions accessible and adaptable to patients living with metastatic cancer, in order to ensure the number of patients obtaining the physical and psychological benefits associated with physical activity is maximised.

It is important to identify the factors which may play a role in the illness experience of metastatic cancer patients and that may contribute to physical inactivity. The purpose of this study was to qualitatively explore the views of men diagnosed with metastatic prostate cancer towards physical activity. Future physical activity interventions may then incorporate this knowledge in order to meet the specific exercise needs and capabilities of patients with metastatic prostate cancer.

Materials and methods

Participants and procedures

Patients with metastatic prostate cancer who were recruited to a randomised control trial examining the effect of exercise on circulating tumour cells were eligible to complete interviews for the present study. Metastatic cancer (also known as advanced or palliative) includes the American Joint Committee on Cancer definition of stage IV cancer [14]. Patients were recruited from oncology clinics at three hospital sites. Inclusion criteria for the randomised control trial are patients ≥18 years and male, a histologically confirmed diagnosis of prostate adenocarcinoma, metastatic disease as confirmed by CT/MRI or by bone scan, stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to recruitment and capable of participating safely in exercise. Exclusion criteria included a history of radical prostatectomy and a previous diagnosis of any other malignant tumour.

The Health Belief Model (HBM) guided the development of interview questions. The HBM framework has been widely accepted as an organising framework which predicts health behaviours by focusing on the attitudes and beliefs of individuals [15]. For example, participants were asked 'What factors, if any, do you think prevent you from engaging in or increasing your physical activity since your cancer diagnosis?' This question was developed to determine barriers to physical activity post diagnosis. Examples of questions in the interview guide are included in Table 1.

Data collection

The first 20 patients recruited to a clinical trial were invited to complete qualitative interviews prior to patient randomisation. Data saturation was used as a guiding principal for sample size, which was determined iteratively. Age, body mass index, waist circumference and burden of metastatic disease were recorded for each participant as part of their baseline randomised controlled trial assessment. Participants also completed a self-report physical activity questionnaire (Physicians' Health Study Assessment). Participants were interviewed using audio-recorded, face-to-face, semi-structured interview format. Each interview lasted between 15 and 20 min. All interviews were carried out by one researcher with 5 years experience in the area of cancer rehabilitation.

Data analysis

All interviews were tape-recorded and transcribed verbatim. Transcripts were analysed using content analysis [16]. Two researchers read each interview script independently. Transcripts were analysed line by line for themes reflecting factors affecting physical activity in men with metastatic prostate cancer. Comparative analysis was conducted with subsequent transcripts to build findings upon themes that had previously emerged. Themes were first subject to broad inclusion so as not to restrict the validity of the data due to premature categorization. As further interviews were analysed, responses were grouped first into subthemes, with those eventually being clustered under applicable broad themes. These were compared, discussed and organised by the same researchers. Data saturation was reached by interview 17. The remaining three interviews were used to confirm and clarify the analysis. Demographic data were entered into an Excel database and analysed descriptively.

Ethical approval

Ethical approval was granted by Saint James's Hospital/Adelaide Meath National Children's Hospital research ethics committee and all participants provided written informed consent to complete interviews.

Results

Twenty patient interviews were completed. All patients who were invited to participate consented to interview. Participant

Table 1 Example questions from the interview guide

Interview question topic	Example question
Self-efficacy	Do you feel could complete as much physical activity as your peers?
Benefits to physical activity participation	What makes you want to be physically active?
Barriers to physical activity participation	What factors, if any, do you think prevent you from engaging in or increasing your physical activity since your cancer diagnosis?
Cues to action	How do your family feel about you participating in regular physical activity?

demographics and clinical characteristics are described in Table 2.

The results of the content analysis were classified into four major themes (Table 3). Quotations reflecting the range of issues that emerged are presented and were selected because they were typical of the insights that participants gave during interviews.

1. Barriers to physical activity

Exercise barriers were mainly related to metastatic cancer and the side effects of cancer treatment including hormone therapy and chemotherapy. Additionally, physical, psychological and environmental barriers to physical activity were mentioned.

Many patients reported symptoms of metastatic disease as barriers to engaging in physical activity 'It was that pain along the bottom of my back that was really stopping me a lot' (P 02), 'I think it was the pains that were obviously beginning to come from the cancer' (P 04). Fatigue also made it difficult for patients to increase their physical activity 'It's difficult when you're feeling tired. I get awful tired. Awful tired those damn hormones' (P 11), 'I find that I get very tired if I try to do exercise' (P 04), 'Since I've started chemo I've lost all my energy' (P 13), 'The chemo was the turning point. No energy. I would walk around the corner with the dog and I would be flat.' (P 14). Other factors such as low mood and low confidence were also reported by patients 'Those hormones. And you know you feel very down with them' (P 11), 'I'll make a fool of myself but no…..I'd say that I won't be able to…' (P 05). Issues around urinary incontinence were also identified as barriers to exercise 'It's quite embarrassing actually you would be out playing badminton and the next minute you would have to run to the toilet' (P 10), 'I have to go straight away. Sometimes I control a little but I have to go straight away.' (P 14). Additionally, the effects of hormone treatment during exercise were mentioned: 'The hot flushes...they vary in terms of intensity. When I get the hot flushes I feel this thing going right up through my body. Pin pricks right up through my body.' (P 14).

Bad weather was mentioned by many as a barrier to exercise 'I hate the weather and I thought of joining the gym locally instead but that's not as good as being out on the road for me' (P 01), 'I haven't been doing anything because of the bad weather' (P 07), 'I don't feel very comfortable walking in the cold.' (P 13). A lack of suitable facilities for exercising due to rural living was also a barrier: 'You have to drive to town to do it because there is no footpaths on the roads and it's too dangerous.' (P 10), 'I try but I'm out in the country' (P 11). Low motivation was another reason for poor physical activity levels: 'I reckon my enthusiasm has gone down eemm to some extent' (P 01), 'I think I should get more done, I should walk more' (P 04), 'It's hard because to motivate yourself to get up and get going' (P 10). Difficulties exercising independently were also identified 'If someone else was doing it I would do it you know that sort of way. If I do it on my own you know…..it's not the best.' (P 18).

2. Benefits of physical activity

Table 2 Participant characteristics

	Total
Age (mean ± SD) years	71 (SD 8.5)
BMI (mean ± SD) Kg/m^2	30.19 (SD 5.37)
Waist circumference (cm ± SD)	104 ± 15.2
Time since cancer diagnosis (Months, median (IQR))	10.5 (6.25–22.25)
Severity of bone metastatic disease *n* (%)	
Minor (1 region affected)	5 (25)
Moderate (2 regions affected)	4 (20)
Major (> 2 regions affected)	11 (55)
Primary treatment *n* (%)	
Radiation therapy	5 (25%)
Hormones	19 (95%)
Achieving aerobic physical activity guidelines (%)	
Yes	9 (45)
No	11 (55)
Physical activity category	
Light (MET-h/wk value < 3)	10 (50%)
Moderate (MET-h/wk between 3 and 5.9)	9 (45%)
Vigorous activities (MET-h/wk value of_≥ 6)	1 (5%)

SD standard deviation, *MET* metabolic equivalent, *h/wk* hours per week

Table 3 Qualitative themes identified

Major themes	Subtheme
Barriers to physical activity	Physical barriers
	Psychological barriers
	Environmental barriers
Benefits of physical activity	Weight loss
	Increased energy
	General feeling of well-being
Reduction in physical activity levels post diagnosis	A disruption to normal daily routine
	Patients unable to overcome barriers to physical activity
Social support for physical activity	Differences in the level of family support for physical activity
	Different perceptions of physical activity levels of peers

When asked about the benefits of physical activity, the majority of patients referred to the general health benefits of physical activity 'It would make me more fitter and it would be something I would look forward to I imagine' (P 016), 'You just feel so much better' (P 019). There was a sense that physical activity facilitated participants to regain a routine and normality 'I would like to be able to get back to what I was doing before' (P 02). Only a small number of the specific health benefits of exercise were reported. Weight loss was most commonly reported, followed by an increase in energy levels. Others referred to benefits of exercise unrelated to physical health 'It keeps me busy' (P 09). Patients reported few specific benefits of exercise related to a cancer diagnosis. Walking, swimming and cycling were the modes of exercise participants felt were of most benefit, 'Maybe a bit of walking…..anything to get the heart pumping.' (P 16).

3. Reduction in physical activity levels post diagnosis

Many patients reported a history of being active, both in their childhood and as an adult prior to their cancer diagnosis. Many patients reported high physical activity levels in the past due to jobs in areas such as farming or the armed forces and from walking or cycling to and from work. Other participants were active mainly for leisure 'Well, I played hockey, field hockey until I was 52 and I played hurling and gaelic football when I was young and I played a lot of tennis' (P 04).

Several patients commented on a recent change in physical activity levels 'I used to be very fit…but that's water under the bridge' (P 15). A significant number of patients described a decrease in physical activity levels after being diagnosed with advanced cancer 'Before I got this diagnosis of the cancer I was walking' (P 08), 'I played badminton actually until February last year' (P 10). Patients describe a decrease in physical activity levels after their diagnosis for many reasons. Due to the high levels of hospital commitments following diagnosis, patients noted a change in physical activity levels 'I started getting hospital appointments and all that kind of stuff and it put me onto a different cycle and I stopped doing the regular exercise' (P 01). Other patients also mentioned the disruption a cancer diagnosis brought to normal routines 'It was just then when I stopped that I never got back to it' (P 05). Some were unsure of the effects of exercise post diagnosis and reported feeling unsure about what physical activity to undertake 'I didn't know whether to exercise or not.' (P 02), 'What are you to say when you have a cancer that has gone into the skeleton? You just don't know. You just keep going as best you can' (P 04).

4. Social support for physical activity

There was a large variation across the study sample in levels of support from family and friends in relation to physical activity. When asked about family attitudes towards their physical activity, half of participants reported their family are very supportive 'They encourage me, like to see me up and about' (P 03), 'They want me to do it' (P 05), 'They (family) want me to (exercise) very much so' (P 04), 'They don't want me lying in bed. They want me to be up going around.' (P 06), 'They say it to me as well ….you're not out on the farm, you have to keep moving….. They would like to see me doing something' (P 11), 'They would be quite agreeable to it. They don't mind seeing me up' (P 16). Alternatively, other participants felt family were indifferent to what physical activity they completed 'They would leave it up to myself.' (P 02), 'I think they would be very uninterested….' (P 01), 'They don't care what I do' (P 06), 'They don't mind what I do' (P 08). Some participants were unsure 'It would depend what it is' (P 07), 'They are happy enough…they don't like to see me on my bike though. Sometimes they say you're too old…….not for me. I don't think so' (P 09). No patients mentioned a diagnosis of metastatic prostate cancer as an issue of concern for family members in relation to physical activity.

The majority of patients felt they were less active than their peers 'I think at the present I would be behind a fair bit' (P 08) or felt that what physical activity they did was not enough.

Also, a large number of participants were not sure how their physical activity levels compared to others 'It's hard for me to know about what I do. I don't really have a bench mark to sort of measure it. I'd say ……. I'm not too bad' (P 04). One patient perceived themselves to be as active as their peers 'I'm normal, I'm exercising as much as anybody else' (P 03). Many patients commented on how they had no way of knowing what exercise or how much exercise others completed 'I don't know what anyone else is doing (P 10), 'I don't see anyone else' (P 11).

Discussion

The purpose of this study was to determine the perceptions of men with metastatic prostate cancer towards physical activity. This study outlines generic and cancer-specific barriers to physical activity perceived by patients with metastatic prostate cancer. Patients associated the time following a diagnosis of advanced cancer with a decline in physical activity levels. Patients identified few health benefits of physical activity, highlighting the need to increase education around physical activity post diagnosis.

Many participants in this study reported a decrease in physical activity levels following a diagnosis of advanced prostate cancer. This is similar to findings in previous studies of patients with early stage breast and colorectal cancer [17, 18]. Patients in this study offered potential explanations for this decline in physical activity levels including the disruption to daily routines caused by multiple hospital visits and the side effects of cancer treatment. These findings are similar to those in previous studies, where an association between common treatments for the management of bone metastases, such as radiation therapy and chemotherapy [19, 20], and a large reduction in physical activity levels [21, 22] were found. There is however a growing body of literature examining the benefits of maintaining and increasing physical activity levels during cancer treatment, including chemotherapy [23, 24], radiation therapy [25, 26] and hormone therapy [27]. Efforts are needed to increase physical activity levels of patients after diagnosis and during the treatment stage of advanced cancer. These could include patient education around the importance of physical activity during this time and the provision of exercise information leaflets, verbal advice or the referral of patients to appropriate exercise services. Previous studies in breast cancer populations have shown that even the provisions of standard public health physical activity recommendations to patients post cancer diagnosis can have long-term effects on physical activity engagement [28, 29].

Study participants reported many barriers to engaging in physical activity. A number of these barriers are similar to those reported in studies of patients with early stage disease and indeed the general population, e.g., difficulty accessing exercise facilities and bad weather [30], e.g., initiating and maintaining a regular exercise regimen [31]; however, participants in this study also described many physical and psychological side effects of metastatic prostate cancer as barriers to engaging in physical activity. The spread of cancer into the bones was a cause of concern for some, leading to uncertainty about the role of exercise. An additional worry centred on problems relating to exercising with poor urinary and bowel control, common in men diagnosed with prostate cancer [32]. These complex presentations reflect why individuals with a cancer diagnosis are considered a special population in terms of exercise prescription [33]. Physical activity barriers have proven to be predictors of exercise behaviour [34] and so each patient reported barrier needs to be examined and addressed carefully in order to optimise the engagement of patients with metastatic cancer in physical activity.

Additionally, adverse symptoms of long-term hormone treatment were highlighted, such as weight gain, which may have also contributed to the high BMI found in this study, and fatigue [35]. Engaging in physical activity which involves resistance and cardiovascular exercise has been shown to have beneficial effects on both fatigue [36] and body composition [37] for men on hormone treatment. The uncertainty reported by patients regarding the type and duration of physical activity suitable for patients with a diagnosis of metastatic cancer further highlights the need for patient education in this area. Patients may benefit from referral to appropriate exercise therapists specialised in the area of oncology to discuss physical activity plans during cancer treatment and recovery. The prescription of exercise by a specialist with oncology-specific education and training is a preference identified by many patients with cancer [38, 39] and will ensure patients with metastatic cancer receive appropriate and achievable exercise plans which consider the relevant physical and psychological side effects of their stage of cancer and cancer treatment [40].

Participants in this study described a large variation in their perceived level of family support for physical activity. A previous study of patients with brain metastases found that despite having full ambulation, 49% of patients preferred completing their physical activity with a spouse, caregiver, family or friend. This suggests patient need for emotional, rather than physical, support from people close to them [41]. A number of patients in the current study commented on the indifference of family members regarding their physical activity levels. Often, families may not discuss physical activity with patients as they feel a need to support the patient's autonomy and also due to the expectation of negative and defensive reactions to suggestions regarding initiating or increasing exercise behaviour [42]. In a review examining the correlates of adults' participation in physical activity, all studies that included a measure of social support for physical activity found a significant positive association with physical activity [43]. For patients diagnosed with cancer, social support may affect attitudes and

normative beliefs about the impact of lifestyle changes on their treatment outcomes [44]. The importance and value of physical activity for patients with metastatic cancer should be discussed with patient's family members. Physical activity consultations for patients diagnosed with cancer may have a role in assisting patients and families to overcome interpersonal issues. Exercise specialists treating patients with metastatic cancer should consider the role of family support when prescribing physical activity programmes to patients.

Clinical implications

This study outlined many physical activity barriers associated with suboptimal activity levels in patients diagnosed with metastatic prostate cancer. Physical activity in patients with metastatic cancer should be encouraged in clinical practice. When symptoms of metastatic prostate cancer are reported as barriers to engaging in physical activity, patients should be referred to the appropriate healthcare professionals for the assessment and management of these symptoms and for guidance on how to exercise according to symptom severity.

Study limitations

All participants in this study had agreed to participate in a randomised control clinical trial involving a physical activity intervention which introduces a substantial self-selection bias and limits the applicability of study findings to all men with metastatic prostate cancer. While this study demonstrated that there are patients with metastatic prostate cancer with a high disease load willing to participate in physical activity interventions, further research is required to explore the issues identified within this study within the wider metastatic cancer population.

Conclusion

Men living with metastatic prostate cancer have unique needs regarding physical activity related to symptoms of both their cancer and cancer treatment. There is a need to increase prompts that encourage patients with metastatic cancer to maintain/increase their physical activity levels post diagnosis. Given the individualised needs of this patient group, referral to a cancer exercise specialist should be considered for the prescription of tailored physical activity programmes.

Acknowledgments The authors would like to acknowledge the assistance and support of the Wellcome Trust/HRB Clinical Research Facility at St. James' Hospital in providing a dedicated environment for the conduct of high quality clinical research activities.

Funding A researcher on this paper (GS) was supported by funding attained through the World Cancer Research Fund [WCRF: 2013/1003, TCD: Award 12799 Project 202370].

Compliance with ethical standards

Ethical approval Ethical approval was granted by Saint James's Hospital/Adelaide Meath National Children's Hospital research ethics committee.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, Oredalen E, Frantzen TL, Lesteberg I, Amundsen L, Hjermstad MJ, Haugen DF, Paulsen O, Kaasa S (2011) Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 16(11):1649–1657. https://doi.org/10.1634/theoncologist.2011-0133
2. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA (2013) Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis 16(4):328–335. https://doi.org/10.1038/pcan.2013.22
3. Courneya KS, Karvinen KH (2007) Exercise, aging, and cancer. Appl Physiol Nutr Metab 32(6):1001–1007
4. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Hjermstad MJ, Kaasa S (2005) Are palliative cancer patients willing and able to participate in a physical exercise program? Palliat Support Care 3(4):281–287
5. Porock D, Kristjanson LJ, Tinnelly K, Duke T, Blight J (2000) An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. J Palliat Care 16(3):30–36
6. Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, Saxton JM, Rosario DJ (2014) Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol 65(5):865–872. https://doi.org/10.1016/j.eururo.2013.09.040
7. Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, Harris SR (2009) Effects of exercise intervention on persons with metastatic cancer: a systematic review. Physiother Can 61(3):141–153. https://doi.org/10.3138/physio.61.3.141
8. Zopf EM, Newton RU, Taaffe DR et al (2017) Associations between aerobic exercise levels and physical and mental health outcomes in men with bone metastatic prostate cancer: a cross-sectional investigation. Eur J Cancer Care 26:e12575. https://doi.org/10.1111/ecc.12575
9. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM (2011) Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol 29(6):726–732. https://doi.org/10.1200/JCO.2010.31.5226
10. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA (2005) Physical activity and survival after breast cancer diagnosis. JAMA 293(20):2479–2486. https://doi.org/10.1001/jama.293.20.2479
11. Cheung WY, Le LW, Gagliese L, Zimmermann C (2011) Age and gender differences in symptom intensity and symptom clusters among patients with metastatic cancer. Support Care Cancer 19(3):417–423. https://doi.org/10.1007/s00520-010-0865-2
12. Lowe SS, Watanabe SM, Baracos VE, Courneya KS (2010) Physical activity interests and preferences in palliative cancer

patients. Support Care Cancer 18(11):1469–1475. https://doi.org/10.1007/s00520-009-0770-8
13. Coleman RE (2006) Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 12(20 Pt 2):6243s–6249s. https://doi.org/10.1158/1078-0432.CCR-06-0931
14. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17(6):1471–1474. https://doi.org/10.1245/s10434-010-0985-4
15. Janz NK, Becker MH (1984) The Health Belief Model: a decade later. Health Educ Q 11(1):1–47. https://doi.org/10.1177/109019818401100101
16. Hsieh HF, Shannon SE (2005) Three approaches to qualitative content analysis. Qual Health Res 15(9):1277–1288. https://doi.org/10.1177/1049732305276687
17. Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, Kriska A, Ballard-Barbash R (2003) Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer 97(7):1746–1757. https://doi.org/10.1002/cncr.11227
18. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, Fuchs CS (2006) Physical activity and survival after colorectal cancer diagnosis. J Clin Oncol 24(22):3527–3534. https://doi.org/10.1200/JCO.2006.06.0855
19. Hartsell WF, Scott CB, Bruner DW, Scarantino CW, Ivker RA, Roach M 3rd, Suh JH, Demas WF, Movsas B, Petersen IA, Konski AA, Cleeland CS, Janjan NA, DeSilvio M (2005) Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 97(11):798–804. https://doi.org/10.1093/jnci/dji139
20. Fizazi K, Beuzeboc P, Lumbroso J, Haddad V, Massard C, Gross-Goupil M, Di Palma M, Escudier B, Theodore C, Loriot Y, Tournay E, Bouzy J, Laplanche A (2009) Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol 27(15):2429–2435. https://doi.org/10.1200/JCO.2008.18.9811
21. Dahele M, Skipworth RJ, Wall L, Voss A, Preston T, Fearon KC (2007) Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manag 33(6):676–685. https://doi.org/10.1016/j.jpainsymman.2006.09.024
22. Ferriolli E, Skipworth RJ, Hendry P, Scott A, Stensteth J, Dahele M, Wall L, Greig C, Fallon M, Strasser F, Preston T, Fearon KC (2012) Physical activity monitoring: a responsive and meaningful patient-centered outcome for surgery, chemotherapy, or radiotherapy? J Pain Symptom Manag 43(6):1025–1035. https://doi.org/10.1016/j.jpainsymman.2011.06.013
23. van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, de Maaker-Berkhof M, Boven E, Schrama J, Geenen MM, Meerum Terwogt JM, van Bochove A, Lustig V, van den Heiligenberg SM, Smorenburg CH, Hellendoorn-van Vreeswijk JA, Sonke GS, Aaronson NK (2015) Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. J Clin Oncol 33(17):1918–1927. https://doi.org/10.1200/JCO.2014.59.1081
24. Swenson KK, Nissen MJ, Henly SJ (2010) Physical activity in women receiving chemotherapy for breast cancer: adherence to a walking intervention. Oncol Nurs Forum 37(3):321–330. https://doi.org/10.1188/10.ONF.321-330
25. Mock V, Dow KH, Meares CJ, Grimm PM, Dienemann JA, Haisfield-Wolfe ME, Quitasol W, Mitchell S, Chakravarthy A, Gage I (1997) Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum 24(6):991–1000
26. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, Malone SC, Wells GA, Scott CG, Slovinec D'Angelo ME (2009) Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol 27(3):344–351. https://doi.org/10.1200/JCO.2007.15.4963
27. Moyad MA, Newton RU, Turn UW, Gruca D (2016) Integrating diet and exercise into care of prostate cancer patients on androgen deprivation therapy. Res Rep Urol 8:133–143. https://doi.org/10.2147/RRU.S107852
28. Vallance JK, Courneya KS, Plotnikoff RC, Dinu I, Mackey JR (2008) Maintenance of physical activity in breast cancer survivors after a randomized trial. Med Sci Sports Exerc 40(1):173–180. https://doi.org/10.1249/mss.0b013e3181586b41
29. Jones LW, Courneya KS, Fairey AS, Mackey JR (2004) Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial. Ann Behav Med 28(2):105–113. https://doi.org/10.1207/s15324796abm2802_5
30. Hefferon K, Murphy H, McLeod J, Mutrie N, Campbell A (2013) Understanding barriers to exercise implementation 5-year post-breast cancer diagnosis: a large-scale qualitative study. Health Educ Res 28(5):843–856. https://doi.org/10.1093/her/cyt083
31. Ng JY, Ntoumanis N, Thogersen-Ntoumani C, Deci EL, Ryan RM, Duda JL, Williams GC (2012) Self-determination theory applied to health contexts: a meta-analysis. Perspect Psychol Sci 7(4):325–340. https://doi.org/10.1177/1745691612447309
32. Glaser AW, Fraser LK, Corner J, Feltbower R, Morris EJ, Hartwell G, Richards M, Wagland R (2013) Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ Open 3(4):e002317. https://doi.org/10.1136/bmjopen-2012-002317
33. Hayes SC, Spence RR, Galvao DA, Newton RU (2009) Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. J Sci Med Sport 12(4):428–434. https://doi.org/10.1016/j.jsams.2009.03.002
34. Ellis T, Boudreau JK, DeAngelis TR, Brown LE, Cavanaugh JT, Earhart GM, Ford MP, Foreman KB, Dibble LE (2013) Barriers to exercise in people with Parkinson disease. Phys Ther 93(5):628–636. https://doi.org/10.2522/ptj.20120279
35. Galvao DA, Taaffe DR, Spry N, Newton RU (2007) Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. Prostate Cancer Prostatic Dis 10(4):340–346. https://doi.org/10.1038/sj.pcan.4500975
36. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, Venner PM, Quinney HA, Jones LW, D'Angelo ME, Wells GA (2003) Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 21(9):1653–1659. https://doi.org/10.1200/JCO.2003.09.534
37. Galvao DA, Nosaka K, Taaffe DR, Spry N, Kristjanson LJ, McGuigan MR, Suzuki K, Yamaya K, Newton RU (2006) Resistance training and reduction of treatment side effects in prostate cancer patients. Med Sci Sports Exerc 38(12):2045–2052. https://doi.org/10.1249/01.mss.0000233803.48691.8b
38. Karvinen KH, Courneya KS, Campbell KL, Pearcey RG, Dundas G, Capstick V, Tonkin KS (2006) Exercise preferences of endometrial cancer survivors: a population-based study. Cancer Nurs 29(4):259–265. https://doi.org/10.1097/00002820-200607000-00001
39. Jones LW, Guill B, Keir ST, Carter K, Friedman HS, Bigner DD, Reardon DA (2007) Exercise interest and preferences among patients diagnosed with primary brain cancer. Support Care Cancer 15(1):47–55. https://doi.org/10.1007/s00520-006-0096-8
40. Hwang JH, Chang HJ, Shim YH, Park WH, Park W, Huh SJ, Yang JH (2008) Effects of supervised exercise therapy in patients

receiving radiotherapy for breast cancer. Yonsei Med J 49(3):443–450. https://doi.org/10.3349/ymj.2008.49.3.443

41. Lowe SS, Danielson B, Beaumont C, Watanabe SM, Courneya KS (2016) Physical activity interests and preferences of cancer patients with brain metastases: a cross-sectional survey. BMC Palliative Care 15(1):7. https://doi.org/10.1186/s12904-016-0083-x
42. Rhudy L, Dose AM, Basford J, Griffin JM, Cheville AL (2015) Caregivers' attitudes toward promoting exercise among patients with late-stage lung cancer. J Community Support Oncol 13(11): 392–398. https://doi.org/10.12788/jcso.0177
43. Trost SG, Owen N, Bauman AE, Sallis JF, Brown W (2002) Correlates of adults' participation in physical activity: review and update. Med Sci Sports Exerc 34(12):1996–2001. https://doi.org/10.1249/01.MSS.0000038974.76900.92
44. Coleman S, Berg CJ, Thompson NJ (2014) Social support, nutrition intake, and physical activity in cancer survivors. Am J Health Behav 38(3):414–419. https://doi.org/10.5993/AJHB.38.3.10

Appendix 5: Published Paper: Physical Activity and Advanced Cancer: The Views of Chartered Physiotherapists in Ireland

PHYSIOTHERAPY THEORY AND PRACTICE
https://doi.org/10.1080/09593985.2017.1422821

Taylor & Francis
Taylor & Francis Group

REPORT

Check for updates

Physical activity and advanced cancer: The views of chartered physiotherapists in Ireland

Gráinne Sheill, BSc PT, MSc[a], Emer Guinan, BSc PT, PhD[a], Linda O Neill, BSc PT, MSc[a], David Hevey, BA, MA, PhD[b], and Juliette Hussey, BSc PT, PhD[a]

[a]Discipline of Physiotherapy, School of Medicine, Trinity College Centre for Health Sciences, Dublin, Ireland; [b]School of Psychology, Trinity College Dublin, Dublin, Ireland

ABSTRACT

Objectives: To investigate Irish chartered physiotherapists' views on physical activity for patients with advanced cancer. ***Methods:*** A mixed methods study design was used. Eligibility criteria included Irish physiotherapists treating patients with advanced cancer. An online survey instrument was created, which included: (1) A quantitative section that explored physiotherapists' views on the role of physical activity for patients with advanced cancer; and (2) A qualitative section that explored physiotherapists' prescription of physical activity for two patient case studies. Quantitative data were analyzed using descriptive statistics, and qualitative data were analyzed using content analysis. ***Results:*** A total of 38 physiotherapists completed the study. In all, 94% (n = 36) of physiotherapists agreed with the statement "being physically active is important for patients with advanced cancer" and 80% (n = 30) stated a need for further information on prescribing physical activity to patients with advanced cancer. A content analysis of case study responses demonstrated physiotherapists have a number of concerns regarding the prescription of physical activity to patients with bone metastasis. Concerns center on patients' increased fracture risk, the presence of osteoporosis and the risk of falls in this patient group. ***Conclusion:*** The majority of physiotherapists perceived physical activity to be of benefit for patients living with advanced cancer. There is a need for more education and training around the prescription of physical activity programs to advanced cancer populations. Physiotherapists' responses suggest patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels post diagnosis.

ARTICLE HISTORY
Received 22 June 2016
Revised 28 September 2016
Accepted 8 April 2017

KEYWORDS
Physical activity; physical therapists; advanced cancer; metastatic cancer

Introduction

Several studies have related higher levels of physical activity during and after cancer treatment with enhanced physical performance, reduced fatigue levels, and improved quality of life (QoL) (Courneya et al., 2003; Dimeo et al., 2003, 1997). Despite this, physical activity participation declines substantially during treatment (Eyigor and Kanyilmaz, 2014) and physical activity levels among cancer survivors are below recommended levels (Guinan, Connolly, Kennedy, and Hussey, 2013; Lynch, 2010). This is a very pertinent issue in the advanced cancer population as physical functioning and physical condition are among the most important determinants of palliative patients' quality of life (Oldervoll et al., 2006). Improved treatment options allow patients to live with advanced or metastatic cancer for longer; however, many patients remain inactive due to the side effects of cancer and its associated treatments (Coleman, 2006). Physical symptoms such as pain, breathlessness, fatigue, and edema are especially common and occur in some combination in virtually all patients with advanced cancer (Solano, Gomes, and Higginson, 2006). Pain, depression, and fatigue are a symptom cluster associated with reduced physical functioning (Laird et al., 2011). Despite this, studies have also shown that exercise training is safe during and after cancer treatment (Brown et al., 2003; Knols et al., 2005; Schmitz et al., 2010) and systematic reviews have determined that both resistance and aerobic activity programs are both safe and beneficial for patients with metastatic disease (Albrecht and Taylor, 2012; Beaton et al., 2009). Additionally, trials have established that patients with a life expectancy of <1 year are willing and able to attend physical activity programs (Oldervoll et al., 2005).

Physiotherapists, also known globally as physical therapists, work closely with patients to alleviate the

CONTACT Gráinne Sheill, BSc PT MSc sheillg@tcd.ie Discipline of Physiotherapy, School of Medicine, Trinity College Centre for Health Sciences, Dublin 8, Ireland.

physical side effects of cancer and its treatment, and encourage physical activity. Physiotherapy involvement in the later and terminal stages of disease can enable patients to improve QoL, as physiotherapists use their knowledge and skills to highlight the importance of physical activity in the management and reduction of cancer related side effects (Okamura, 2011). To date, there are no exercise guidelines specifically for patients with advanced or metastatic cancer. It is recommended that all patients with cancer (receiving treatment, following treatment, curative, and palliative) complete 150 min/week moderate-intensity aerobic exercise or 75 min/week of vigorous exercise, as prescribed for a healthy population (Thompson, Arena, Riebe, and Pescatello, 2013). However, due to the complex symptoms of an advanced state of disease, many patients with metastatic disease require tailored exercise guidance (Cormie et al., 2013). For example, patients with bone metastasis require exercise programs that consider the level of morbidity associated with the location and type of their metastatic lesion. As a consequence of their individual needs, many patients seek out, or are referred to physiotherapists for physical activity recommendations and guidance.

Physiotherapists make physical activity recommendations and guide patients through cancer rehabilitation programs based on their clinical knowledge and the best available evidence (Wolin et al., 2012). The lack of specific guidelines regarding exercise prescription for patients with advanced cancer is noticeable and may have implications for chartered physiotherapists practicing in this area in Ireland and further afield. The prescription of exercise and physical activity to patients with advanced cancer in both inpatient and outpatient settings may present many challenges to therapists due to the complexity of this disease presentation and the concurrent pharmaceutical management. The views held by physiotherapists have previously shown an association with clinical practice behavior (Bishop, Foster, Thomas, and Hay, 2008). The Health Belief Model (HBM) is a framework that may be used to explore the views of physiotherapist in order to gain a greater understanding of the current clinical practice around prescribing physical activity to patients with advanced cancer. The HBM suggests that a set of attitudes or beliefs lead to behavior (Janz and Becker, 1984). This study will use the constructs of the HBM to examine physiotherapists' views of physical activity, including its benefits and barriers, for the advanced cancer population. Physiotherapists' self-efficacy around prescribing physical activity to this patient group will be examined, as well as any perceived cues to action or activation strategies which may trigger increased physical activity levels in this patient population (Deo, Nayak, and Rajpura, 2013; Rosenstock and Hochbaum, 1961). This study aims to: (1) Describe Irish chartered physiotherapists' views on the role of physical activity for patients with advanced cancer; and (2) Explore physiotherapists' prescription of physical activity for two case studies of patients with advanced cancer.

Materials and methods

Participants

The survey link and research information leaflet were sent to the physiotherapy managers of the eight designated cancer centers in Ireland (four in Dublin, and one in each of Waterford, Limerick, Cork, and Galway) for distribution to all physiotherapists working in these centers. The Irish Society for Chartered Physiotherapists office also distributed the survey among the national clinical interest groups for Chartered Physiotherapists in Oncology and Palliative Care (n = 55) and Chartered Physiotherapists in the Community (n = 113). Only physiotherapists treating patients with advanced cancer were asked to complete the online survey. The study protocol was approved by the Trinity College Faculty of Health Sciences Ethics Committee.

Study instrument

Using an online survey service (via SurveyMonkeyTM, SurveyMonkey.com, LLC, Palo Alto, CA, USA) an anonymous questionnaire was created. The survey included demographic questions; 10 attitude questions based on the guiding principles of the Health Belief Model (Janz and Becker, 1984), and two case study questions. Demographic information was collected relating to the physiotherapist's job title, years of experience, and place of work. Physiotherapists' views of prescribing physical activity to this population were assessed by 10 statements rated on a 7-point Likert scale, ranging from "strongly agree" to "strongly disagree." The items assessed included statements on the benefits and safety of exercise for this population.

The survey also included two patient case studies. These case studies were specifically designed by the research team to represent typical advanced cancer patients referred for physiotherapy in a national clinical center.

Case study 1

Patient 1 is 86 years old with widespread axial metastases secondary to prostate cancer. He has few

comorbidities and has been active all his life. During his consultation he mentions to you that he plans on remaining active and continuing activities, which include manual labor in the garden and playing golf every day.

Case study 2

Patient 2 has stage IV prostate cancer with bone metastases to his proximal femur and pelvis. He has a poor relationship with physical activity and multiple comorbidities. He feels that his diagnosis with cancer is another reason to limit his physical activity.

Physiotherapists were asked to provide physical activity recommendations for patients, as well as outline any concerns they had relating to physical activity in the cases provided. All response data was stored on a password accessed server and the survey was live for a 6-week period.

Analysis

Data was exported to SPSS for analyses. Physiotherapists' views toward recommending exercise were analyzed using descriptive statistics. Text-based responses to open-ended questions related to the case studies were analyzed using content analysis (Hsieh and Shannon, 2005). In accordance with the aims of the study, analysis focused on physical activity recommendations and concerns around physical activity. The author read a document comprising all participant responses several times to permit familiarization with the data and to identify initial patterns. An initial coding scheme was developed after the first 10 responses that guided the coding of all remaining responses. Codes were then sorted into emerging categories based on relations between codes and then summarized into emerging themes. To increase the rigour of the analysis, a second author (LON) analyzed all responses independently and combined results with the first author. There were very high levels of agreement in the coding of categories between the two researchers, with no instances of significant disagreement.

Results

Therapists information

A total of 38 physiotherapists responded to the survey (Table 1). Of this, the majority of physiotherapists were senior physiotherapists (physiotherapists holding a minimum of three years' post qualification clinical experience), followed by basic grade or entry level physiotherapists. A small proportion of respondents were clinical specialists (physiotherapists holding a minimum of 5 years' post qualification clinical experience and a postgraduate qualification relevant to the post) or managers. The majority of physiotherapists were qualified between 10 and 20 years (n = 16 (42%)) or over 20 years (n = 11 (29%)) followed by therapists qualified between 5–10 years (n = 6 (16%)) or less than 5 years (n = 5 (13%)).

Table 1. Participant characteristics.

Physiotherapy Grade	Number of Respondents (Percentage)
Basic Grade	8 (21%)
Senior	25 (65%)
Clinical Specialists	2 (6%)
Managers	3 (8%)
Area of Work	
Hospital Setting	13 (34%)
Community Setting	20 (53%)
Private Practice	1 (3%)
Hospice Care	4 (10%)

Views toward physical activity

The vast majority of physiotherapists agreed with the statement "being physically active is important for patients with advanced cancer" (Table 2). Additionally, a high proportion of physiotherapists agreed that patients with advanced cancer are capable of completing physical activity programs and also reported prescribing physical activity to this patient population regularly (Table 2). In response to a statement about how confident physiotherapists felt when prescribing exercise to patients with advanced cancer, a large number of physiotherapists agreed that they were confident however a high number of physiotherapists also agreed there is a need for further information on prescribing physical activity recommendations to patients with advanced cancer. Physiotherapists did not strongly agree that there are cues to action (e.g., such as encouragement from friends and family) that encourage patients with advanced disease to increase physical activity levels (Table 2).

Case study responses

Case study 1

Prescribing physical activity. Physiotherapists outlined the importance of patients maintaining their physical activity levels:

Table 2. Physiotherapists' views toward physical activity and advanced cancer.

Question:	Strongly Agree (n)	Mostly/Somewhat Agree (n)	Neither Agree or Disagree (n)	Somewhat/ Mostly Disagree (n)	Strongly Disagree (n)
Perceived benefits and barriers:					
In my opinion being physically active is important for patients with advanced cancer	**11** (31%)	**22** (63%)	**1** (3%)	**1** (3%)	**0** (0%)
I feel that patients with advanced cancer are capable of completing physical activity programs	**9** (26%)	**23** (66%)	**1** (3%)	**2** (6%)	**0** (0%)
I feel patients with advanced cancer come to me for physical activity recommendations	**4** (11%)	**19** (54%)	**3** (9%)	**9** (26%)	**0** (0%)
In my opinion increasing physical activity levels in patients with advanced cancer is safe	**6** (17%)	**23** (66%)	**2** (6%)	**3** (9%)	**1** (3%)
I find providing physical activity recommendations to patients with advanced disease is usually well received	**2** (6%)	**24** (69%)	**2** (6%)	**7** (20%)	**0** (0%)
Cues to action:					
I feel patients with advanced cancer believe they should remain physically active	**3** (9%)	**15** (43%)	**4** (11%)	**13** (38%)	**0** (0%)
I feel patients with advanced cancer will follow the advice of physical activity recommendations given	**0** (0%)	**22** (63%)	**6** (17%)	**7** (20%)	**0** (0%)
I find the families and friends of patients with advanced cancer encourage physical activity	**1** (3%)	**16** (45%)	**6** (17%)	**11** (31%)	**1** (3%)
Self-Efficacy:					
I am confident in my ability to prescribe exercise to patients with advanced cancer	**8** (23%)	**19** (54%)	**3** (9%)	**5** (14%)	**0** (0%)
I regularly prescribe physical activity recommendations to patients with advanced cancer	**10** (29%)	**20** (57%)	**3** (9%)	**2** (6%)	**0** (0%)

Note: Totals may not equivalent to 100% because of rounding.

> *"I feel physical activity is an important adjunct to this man's treatment"* (Participant (P) 17, Case Study (CS) 1).

Engaging in physical activity was seen by another respondent as:

> *"paramount to his mental health"* (P4, CS1).

When discussing exercise prescription, physiotherapists referenced the existing exercise guidelines for all cancer patients:

> *"I would encourage him to be active for at least 30 mins 5 times per week and working to an intensity in which he is slightly puffed"* (P19, CS1).

Many also stated that the patient should gauge exercise tolerance by common symptoms:

> *'We would discuss pacing activities within his limits of pain and energy levels'* (P7, CS1).

Concerns related to physical activity. Numerous respondents reported some concern when prescribing physical activity to this patient:

> *"I would feel relatively comfortable although concerned with his age, mets and demands of golf"* (P04, CS1).

Concern centered on the possibility of increasing harm to the patient, in many cases due to the presence of bone metastasis.

> *"There is a risk of bone fracture if activity is not properly prescribed"* (P23, CS1).

Physiotherapists suggested adapting this patient's current activities to ensure safety and comfort for patients:

> *"may need to modify some of how he does his garden"* (P18, CS1),
>
> *"he may have to modify some tasks"* (P10, CS1).

Only two physiotherapists suggested what these modifications may entail:

> *"consider positioning, use of equipment"* (P22, CS1)
>
> *"positions to reduce strain on his back, possibly wearing a corset for some activities"* (P25, CS1).

While some physiotherapists mentioned the modification of activities others suggested limiting any high intensity activities:

> *"Not necessarily to discourage him but to set boundaries that he should be aware of when exercising"* (P16, CS1).

Responses by some physiotherapists demonstrated uncertainty about how to gauge intensity:

> *"I would wonder if I am working this patient at too high or low an intensity to get benefit/harm from exercise"* (P13, CS1).

Case study 2

Prescribing physical activity. Physiotherapists were happy to initiate a discussion with this patient about physical activity:

> *"I would feel very comfortable discussing physical activity options"* (P26, CS2).

Activities to enable functional independence and activities that were enjoyable for this patient were encouraged. Discussing physical activity was seen by 30% (11/38) of physiotherapists as an opportunity to educate this patient on the benefits of physical activity for managing cancer related symptoms and side effects of treatment. Physiotherapists recognized there may be an element of fear preventing this patient from increasing his physical activity:

> *"This patient may be frightened by his bone METS"* (P20, CS2).

Responses highlighted that with encouragement and reassurance the patient may increase physical activity levels:

> *"Hopefully with education and guidance, he may be confident to exercise"* (P23, CS2).

Concerns related to physical activity. In case study 2, physiotherapists indicated a need to complete a multifactorial assessment before prescribing increases in physical activity. Physiotherapists felt the patient's pre-morbid status, fatigue levels, pain levels, and risk of cachexia all needed thorough assessment. The theme of causing harm to the patient arose in responses to this case study also. Around 18% (7/38) of physiotherapists reported a need to discuss the patient's exercise capacity with the medical team or GP prior to the prescription of physical activity:

> *"Risk of fracture would need to be discussed at MDT level before I would discuss PA with this patient"* (P19, CS2).

Concern related to physical activity prescription with this patient again centered on bone fragility: *"he is at increased risk of osteoporosis and fractures"* (P11, CS2).

Pain was mentioned as an indication to limit activity by many physiotherapists:

> *"Stop if there is any pain or discomfort"* (P7, CS2).

> *"I would be guided by pain in his pelvis/hip area"* (P18, CS2).

There were varying responses regarding the amount of weight bearing this patient could tolerate during physical activity:

> *"The type of exercise would need to consider weight bearing limitations and what alternative options there are"* (P22, CS).

> *"He would be suitable for non-weight bearing activities"* (P25, CS2).

While many physiotherapists discussed potential aerobic activities suitable for patients, a small percentage of physiotherapists mentioned concerns in relation to prescribing resistance exercise for this patient:

> *"Functional strength training without specific weight resistance exercise"* (P24 CS2).

> *"Activity prescribed would be based on more functional activity rather than specific weight resistance exercise"* (P25 CS2).

Discussion

The majority of physiotherapists perceived physical activity to be of great benefit for patients living with advanced cancer. Despite the known benefits of remaining physically active there was some ambiguity over the optimal prescription of physical activity to this population. The complex nature of prescribing physical activity to this patient group was a theme evident throughout qualitative responses. Physiotherapists' perceived cues to action suggest that patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels.

Physiotherapists expressed varying levels of confidence in prescribing physical activity to patients with metastatic disease. This may result in poor implementation of the positive findings of previous studies in the clinical setting (Albrecht and Taylor, 2012; Beaton et al., 2009). Despite the growing body of evidence, physiotherapists reported much uncertainty regarding the optimal physical activity parameters for this patient group. While some exercise recommendations given by participants reflected the results of newly established research, others reflected older practices in the area of cancer exercise therapy. The high proportion of respondents working clinically for over 10 years may have influenced their views toward physical activity. Many treatment options for patients with cancer have developed during this time, as have advances in exercise prescription (Cormie et al., 2013; Okamura, 2011). In the past, patients with advanced cancer were excluded from many physical activity programs due to the risks associated with bone metastasis (Adamsen et al., 2009). There are now an increasing number of clinical trials in the advanced cancer population, including patients with bone metastasis (Bourke et al., 2011, 2014; Cheville et al., 2010; Lowe, Watanabe, Baracos, and Courneya, 2013; Oldervoll et al., 2011; Temel et al., 2009). Aerobic exercise programs of up to 12 weeks duration have been completed by patients with advanced cancer, with no adverse events reported (Quist et al., 2012). Despite this, patients were perceived by physiotherapists as highly susceptible to injury due to their advanced stage of disease. The recommendations of clinical studies in this area should be used by

physiotherapists to inform physical activity prescription to similar patient groups in clinical practice.

While physiotherapists perceived physical activity to be of benefit to patients, multiple barriers to prescribing physical activity emerged in qualitative responses. Resistance programs were not encouraged by physiotherapists in both case studies due to concerns about pathological fractures. Despite this, recent studies have shown very promising results in trials involving resistance exercise programs for patients with metastatic disease. Perceived barriers are the strongest and most significant determinant of healthcare related behavior, and it is important that the barriers reported by physiotherapists are addressed (Orji, Vassileva, and Mandryk, 2012). There is a need for more education and training around methods of adapting resistance programs for advanced cancer populations, as implemented in previous clinical studies (Cormie et al., 2013; Temel et al., 2009). There was also uncertainty among physiotherapist relating to the prescription of weight bearing activity to this patient group. No differences in the rate of pathological fracture between patients completing weight bearing or non-weight bearing activity were reported in previous studies (Bunting and Shea, 2001) and pain free weight bearing activity should be encouraged (Riccio, Wodajo, and Malawer, 2007). The outcomes of previous research provides positive evidence for the prescription of appropriately designed and supervised resistance and weight bearing activities to patients with advanced cancer. Increased awareness of this research may help to decrease physiotherapists' perceived barriers to prescribing physical activity. Educational efforts targeting physiotherapists concerns and misconceptions about the prescription of physical activity for patients with advanced disease may help to reduce the level of concern related to prescribing physical activity in this population. In-service training and journal clubs on the topic of physical activity and advanced disease could be used to increase physiotherapist's exposure to the evolving medical literature in this area.

Physiotherapists' perceived cues to action suggest patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels. Given the importance of physical activity in cancer control physiotherapists have an increasingly important role in introducing patients to an exercise environment, but also in educating both patients and their carers on the important role of physical activity in maintaining and optimizing physical function (Courneya and Friedenreich, 2007). Responses in this study indicate that further efforts are needed to educate patients living with advanced cancer on the role of exercise in managing symptoms and improving function. Additionally, physiotherapists' perceptions of patients' families and friends' supportiveness for physical activity suggest that education efforts should also extend to this group. Consultation with a physiotherapist may serve as an important cue to action for patients with advanced disease to maintain or increase physical activity levels, as advice on the benefits of exercise can be shared and discussed. Additional cues to action are also needed. A previous study of the attitudes of Canadian oncologists showed a relatively low proportion of oncologists (29.5%) felt that their patients were capable of exercising during treatment (Jones, Courneya, Peddle, and Mackey, 2005). All healthcare professionals can act as external triggers to encourage patients to increase physical activity levels. Physiotherapists should advocate for the role of physical activity in advanced disease and encourage clinicians to promote physical activity in this population (Daley et al., 2008).

Study limitations

A detailed medical history was not provided for the case studies provided in this article. The provision of more detail relating to case studies may have influenced physiotherapist responses regarding physical activity prescription. The case study was generated specifically for use in this research and its validity requires additional testing as no pilot study was conducted on the material.

Conclusion

The majority of physiotherapists perceived exercise to be of great benefit for patients living with advanced cancer, and regularly prescribe physical activity to this patient group. Despite this, physiotherapists reported ambiguity over the optimal parameters for physical activity prescription. More work is needed on disseminating the results of research in this area among physiotherapists. Physiotherapists' perceived cues to action suggest patients with advanced cancer have limited exposure to factors that may prompt increased physical activity levels. Physiotherapists should advocate for the benefits of physical activity for patients with advanced disease.

Declaration of interest

The authors report no declarations of interest.

Funding

Gráinne Sheill was supported by funding attained through the World Cancer Research Fund [WCRF: 2013/1003, TCD: Award 12799 Project 202370].

References

Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D, Baadsgaard MT, Vistisen K, Midtgaard J, Christiansen B, et al 2009 Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: Randomised controlled trial. BMJ 339: b3410.

Albrecht TA, Taylor AG 2012 Physical activity in patients with advanced-stage cancer: A systematic review of the literature. Clinical Journal of Oncology Nursing 16: 293–300.

Beaton R, Pagdin-Friesen W, Robertson C, Vigar C, Watson H, Harris SR 2009 Effects of exercise intervention on persons with metastatic cancer: A systematic review. Physiotherapy Canada 61: 141–153.

Bishop A, Foster NE, Thomas E, Hay EM 2008 How does the self-reported clinical management of patients with low back pain relate to the attitudes and beliefs of health care practitioners? A survey of UK general practitioners and physiotherapists. Pain 135: 187–195.

Bourke L, Doll H, Crank H, Daley A, Rosario D, Saxton JM 2011 Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. Cancer Epidemiology Biomarkers and Prevention 20: 647–657.

Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, Saxton JM, Rosario DJ 2014 Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: A randomised controlled trial. European Urology 65: 865–872.

Brown JK, Byers T, Doyle C, Coumeya KS, Demark-Wahnefried W, Kushi LH, Mctieman A, Rock CL, Aziz N, Bloch AS, et al; American Cancer Society 2003 Nutrition and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices. CA: A Cancer Journal for Clinicians 53: 268–291.

Bunting RW, Shea B 2001 Bone metastasis and rehabilitation. Cancer 92: 1020–1028.

Cheville AL, Girardi J, Clark MM, Rummans TA, Pittelkow T, Brown P, Hanson J, Atherton P, Johnson ME, Sloan JA, et al 2010 Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well-being. American Journal of Physical Medicine and Rehabililitation 89: 611–619.

Coleman RE 2006 Clinical features of metastatic bone disease and risk of skeletal morbidity. Clinical Cancer Research 12: 6243s–6249s.

Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA 2013 Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer and Prostatic Diseases 16: 328–335.

Courneya KS, Friedenreich CM 2007 Physical activity and cancer control. Seminars in Oncology Nursing 23: 242–252.

Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Fairey AS 2003 A randomized trial of exercise and quality of life in colorectal cancer survivors. European Journal of Cancer Care 12: 347–357.

Daley AJ, Bowden SJ, Rea DW, Billingham L, Carmicheal AR 2008 What advice are oncologists and surgeons in the United Kingdom giving to breast cancer patients about physical activity? International Journal of Behavioral Nutrition and Physical Activity 5: 46.

Deo P, Nayak R, Rajpura J 2013 Women's attitudes and health beliefs toward osteoporosis screening in a community pharmacy. Journal of Osteoporosis 2013: 650136.

Dimeo FC, Schwartz S, Fietz T, Wanjura T, Boning D, Thiel E 2003 Effects of endurance training on the physical performance of patients with hematological malignancies during chemotherapy. Supportive Care in Cancer 11: 623–628.

Dimeo FC, Tilmann MH, Bertz H, Kanz L, Mertelsmann R, Keul J 1997 Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. Cancer 79: 1717–1722.

Eyigor S, Kanyilmaz S 2014 Exercise in patients coping with breast cancer: An overview. World Journal of Clinical Oncology 5: 406–411.

Guinan EM, Connolly EM, Kennedy MJ, Hussey J 2013 The presentation of metabolic dysfunction and the relationship with energy output in breast cancer survivors: A cross-sectional study. Nutrition Journal 12: 99.

Hsieh HF, Shannon SE 2005 Three approaches to qualitative content analysis. Qualitative Health Research 15: 1277–1288.

Janz NK, Becker MH 1984 The health belief model: A decade later. Health Education Quarterly 11: 1–47.

Jones LW, Courneya KS, Peddle C, Mackey JR 2005 Oncologists' opinions towards recommending exercise to patients with cancer: A Canadian national survey. Supportive Care in Cancer 13: 929–937.

Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G 2005 Physical exercise in cancer patients during and after medical treatment: Asystematic review of randomized and controlled clinical trials. Journal of Clinical Oncology 23: 3830–3842.

Laird BJ, Scott AC, Colvin LA, Mckeon AL, Murray GD, Fearon KC, Fallon MT 2011 Pain, depression, and fatigue as a symptom cluster in advanced cancer. Journal of Pain and Symptom Management 42: 1–11.

Lowe SS, Watanabe SM, Baracos VE, Courneya KS 2013 Home-based functional walking program for advanced cancer patients receiving palliative care: A case series. BMC Palliative Care 12: 22.

Lynch BM 2010 Sedentary behavior and cancer: A systematic review of the literature and proposed biological mechanisms. Cancer Epidemiology, Biomarkers and Prevention 19: 2691–2709.

Okamura H 2011 Importance of rehabilitation in cancer treatment and palliative medicine. Japanese Journal of Clinical Oncology 41: 733–738.

Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, Oredalen E, Frantzen TL, Lesteberg I, Amundsen L, et al 2011 Physical exercise for cancer patients with advanced disease: A randomized controlled trial. Oncologist 16: 1649–1657.

Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Hjermstad MJ, Kaasa S 2005 Are palliative cancer patients willing and able to participate in a physical exercise program? Palliative and Supportive Care 3: 281–287.

Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Wiken AN, Hjermstad MJ, Kaasa S 2006 The effect of a physical

exercise program in palliative care: A Phase II study. Journal of Pain and Symptom Management 31: 421–430.
Orji R, Vassileva J, Mandryk R 2012 Towards an effective health interventions design: An extension of the health belief model. Online Journal of Public Health Informatics 2012: 4.
Quist M, Rorth M, Langer S, Jones LW, Laursen JH, Pappot H, Christensen KB, Adamsen L 2012 Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: A pilot study. Lung Cancer 75: 203–208.
Riccio AI, Wodajo FM, Malawer M 2007 Metastatic carcinoma of the long bones. American Family Physician 76: 1489–1494.
Rosenstock IM, Hochbaum GM 1961 Some principles of research design in public health. American Journal of Public Health and the Nations Health 51: 266–277.
Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, et al; American College of Sports Medicine 2010 American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine and Science in Sports and Exercise 42: 1409–1426.
Solano JP, Gomes B, Higginson IJ 2006 A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. Journal of Pain and Symptom Management 31: 58–69.
Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, Lynch TJ, Christiani DC, Smith MR 2009 A structured exercise program for patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology 4: 595–601.
Thompson PD, Arena R, Riebe D, Pescatello LS; American College of Sports Medicine 2013 ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. Current Sports Medicine Reports 12: 215–217.
Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH 2012 Implementing the exercise guidelines for cancer survivors. Journal of Supportive Oncology 10: 171–177.

Appendix 6: Published Paper: Physical Activity and Advanced Cancer: The views of Oncology and Palliative Care Physicians in Ireland

Ir J Med Sci
DOI 10.1007/s11845-017-1677-x

ORIGINAL ARTICLE

Physical activity and advanced cancer: the views of oncology and palliative care physicians in Ireland

G. Sheill[1] · E. Guinan[2] · L. O. Neill[1] · D. Hevey[3] · J. Hussey[1]

Received: 26 April 2017 / Accepted: 21 August 2017

Abstract

Background Physical activity (PA) levels play an important role in maintaining the quality of life and enhancing the physical function of advanced cancer patients. A brief exercise prompt by physicians can increase PA levels of patients diagnosed with cancer.

Aims This study explores the views of Irish oncology and palliative care physicians towards PA for patients with advanced cancer.

Methods A web-based survey with closed- and open-ended questions was used to explore physicians' views. The survey presented a Likert-style questionnaire and open text responses to two patient case studies. Quantitative data were analysed using descriptive statistics, and qualitative data were analysed using content analysis.

Results Forty participants completed the study, a response rate of 41%. Responding physicians acknowledged the importance of physical activity for patients with advanced cancer. Twenty-six physicians (67%) agreed that patients look to them for PA recommendations and 30 physicians (77%) indicated a need for more information on providing PA recommendations. Case study responses highlighted concerns relating to PA prescription for patients with bone metastases including the aggravation of symptom control and increased fracture risk.

Conclusions The results of this study identify a need for physician education on providing PA recommendations for patients with advanced cancer. Concerns over the prescription of PA to patients with bone metastases highlight the need to disseminate the evidence on the benefits of PA for patients with metastatic cancer to healthcare professionals.

Keywords Advanced cancer · Exercise · Metastases · Physicians · Survey

✉ G. Sheill
sheillg@tcd.ie

E. Guinan
emguinan@tcd.ie

D. Hevey
heveydt@tcd.ie

J. Hussey
jmhussey@tcd.ie

[1] Discipline of Physiotherapy, School of Medicine, Trinity College Centre for Health Sciences, James's Street, Dublin 8, Ireland

[2] School of Medicine, Trinity College Centre for Health Sciences, James's Street, Dublin 8, Ireland

[3] School of Psychology, Trinity College Dublin, College Green, Dublin 2, Ireland

Introduction

Patients receiving or completing treatment for advanced cancer have substantially lower physical activity (PA) levels than the general population. In one study that examined the PA levels of 71 patients with metastatic breast cancer, participants attained only half of the steps per day achieved by age-matched healthy controls (5434 ± 3174 vs. 9635 ± 3327) [1]. Additionally, 85% of participants did not achieve > 8000 steps a day: the level at which most health benefits are achieved in older populations [2]. Systematic reviews provide evidence that higher PA levels in patients with advanced cancer are associated with greater quality of life and improved physical status [3, 4]. Therefore, there is a need to explore ways to maximise the PA levels of patients at this stage of the cancer trajectory.

Mounting evidence suggests that oncologists may play an important role in enhancing exercise levels in patients with

Published online: 31 August 2017

cancer [5]. The majority of patients with cancer prefer oncologist-initiated exercise discussions to discussions they initiate themselves [6]. However, a UK study found 56% of breast care oncologists and surgeons did not routinely discuss PA with their patients [7]. Similarly, in a US study, 38% of oncologists and surgeons reported that they did not enquire about patients' activity levels [8]. Collaboration with physicians around PA goals has been shown to improve patients' healthcare outcomes [9]. A single blind randomised controlled trial demonstrated that a brief 30 s oncologist recommendation to exercise during treatment consultations significantly increased PA in patients with newly diagnosed breast cancer by a mean of 3.4 MET-h per week (95% CI 0.7–6.1 MET-h per week) [10].

Oncologists may also be an important source of motivation for patients living with advanced cancer. Studies examining the attitudes of oncology care providers towards recommending exercise for patients with early-stage cancer have identified limited knowledge on how or where to refer a patient to exercise and safety concerns as the main barriers to discussion about exercise [11, 12]. However, there is little information available regarding oncologists' attitudes towards recommending PA to patients with advanced stages of disease. Given the many physical and psychological side effects of advanced cancer, oncologists' attitudes towards this group may differ from the attitudes towards prescribing PA to patients with early-stage disease. Additionally, the presence of bone metastases in many patients with advanced cancer may affect the perceptions of oncologists around the safety of exercise in this population. The aims of this study were to determine the beliefs of Irish physicians regarding PA recommendations for patients with advanced cancer and to explore any potential concerns regarding PA engagement in this population using a scenario-based survey.

Methods

The study protocol was approved by the Trinity College Dublin Faculty of Health Sciences Ethics Committee (Ref: 20150609).

The study was conducted among a convenience sample of consultant radiation or medical oncologists in Ireland or members of the Irish palliative care consultants group. Physicians were senior doctors who had completed speciality training in the area of oncology or palliative care.

An anonymous online survey (via SurveyMonkey.com, LLC, San Mateo, CA, USA) was created. Participants received the survey by email, via contact details listed in the Irish medical directory or palliative care group. Completion of the survey questionnaire was considered to be implied consent to participate. All response data was stored on a password-accessed server. A reminder email was sent at 4 weeks.

The survey included demographic questions, ten attitude questions (rated on a 7-point Likert scale, ranging from 'strongly agree' to 'strongly disagree'), and two case study questions involving patients with bone metastases. These two contrasting case studies were chosen as they were based on typical presentations of patients with bone metastases seen previously in an outpatient oncology clinic in a national cancer centre.

Case study 1

Patient 1 is 86 years old with widespread axial metastases secondary to prostate cancer. He has few co-morbidities and has been active all his life. During his consultation, he mentions that he plans on remaining active and continuing activities, which include manual labour in the garden and playing golf every day.

Case study 2

Patient 2 has stage IV prostate cancer with bone metastases to his proximal femur and pelvis. He has a poor relationship with physical activity and multiple co-morbidities. He feels that his diagnosis with cancer is a reason to limit his physical activity.

Physicians were asked to provide open text comments describing whether they would be happy to provide PA recommendations for the patients and to outline concerns, if any, relating to physical activity prescription in the cases provided. An open-ended text box was left at the end of the survey for additional comments regarding exercise prescription for patients with advanced cancer.

Descriptive data are presented as the mean (standard deviation (SD)) for continuous data and frequency (percentage) for categorical data. Text-based responses to open-ended questions related to the case studies were analysed using content analysis [13]. Each response was coded independently by two of the authors, and codes were compared for interrater agreement.

Results

A total of 98 radiation and medical oncologists and palliative care physicians were contacted and 40 responses were received, a response rate of 41%. Details of the demographic profile of participants are presented in Table 1. The majority of respondents were specialised in palliative care (57%, $n = 23$) and were practicing for over 10 years (82%, $n = 32$). The majority of physicians (55%) reported discussing PA with over half of their patient caseload.

Table 2 provides a summary of physician's responses to the structured questionnaire. All physicians agreed with statements 1 and 2 that PA is important and safe for patients with

Table 1 Demographic characteristics of participants

Variable	Number	Percent
Speciality		
Radiation oncology	9	23
Medical oncology	8	20
Palliative care	23	57
Number of years practicing		
1–5 years	1	3
5–10 years	7	17
10–20 years	19	48
Over 20 years	13	32
Primary tumour group		
Breast	5	22
Genitourinary	6	26
Multiple	12	52
Primary tumour group not identified	17	42
Number of physicians initiating discussions about PA during consultations		
With 0–25% of patients	2	5
With 25–50% of patients	14	35
With 50–75% of patients	10	25
With 75–100% of patients	12	30
No response given	2	5

advanced cancer. The majority of physicians (67%, n = 26) agreed patients look to them for PA recommendations and 74% (n = 23) felt that patients would follow any PA recommendations given. Less than half of physicians (44%, n = 17) agreed that the family and friends of patients encourage PA. A large proportion of physicians (77%, n = 30) expressed a need for more information on providing PA recommendations to this patient cohort.

Common concerns reported by physicians in case studies examining the prescription of exercise to metastatic populations are detailed in Table 3. Further information on responses is described below.

Case study 1

All physicians were happy to discuss PA with this patient. They emphasised the need for this patient to continue to maintain daily activity levels. "I would routinely encourage patients to maintain existing levels of physical activity if they feel they are able" (PHY09). Physicians described the many benefits associated with prescribing PA including limiting the side effects of treatments, reducing cardiovascular risk, weight management, limiting cachexia/muscle loss and fatigue. There was disagreement among physicians about the suitability of weight bearing exercise for this patient "On ADT there is a risk of muscle loss and osteopenia so weight bearing exercise is important" (PHY011), "(he) would need not to engage in

Table 2 Physicians attitudes towards physical activity

	Strongly agree	Mostly agree	Somewhat agree	Neither agree or disagree	Somewhat disagree	Mostly disagree	Strongly disagree
In my opinion being physically active is important for patients with advanced cancer	22 (56%)	14 (36%)	2 (5%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
In my opinion being physically active is safe for patients with advanced cancer	8 (21%)	26 (67%)	5 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
My fellow clinicians feel physical activity is important for patients with advanced cancer	5 (13%)	16 (41%)	9 (23%)	7 (18%)	0 (0%)	1 (3%)	1 (3%)
I feel that patients with advanced cancer believe they should remain physically active	2 (5%)	8 (21%)	17 (44%)	1 (3%)	10 (26%)	1 (3%)	0 (0%)
I feel that patients with advanced cancer look to me for physical activity recommendations	1 (3%)	12 (31%)	13 (33%)	8 (21%)	3 (8%)	2 (5%)	0 (0%)
I find that providing physical activity recommendations to patients with advanced disease is usually well received	4 (10%)	16 (41%)	12 (31%)	4 (10%)	3 (8%)	0 (0%)	0 (0%)
I feel that patients with advanced cancer will follow the physical activity recommendations given	2 (5%)	7 (18%)	20 (51%)	4 (10%)	5 (13%)	1 (3%)	0 (0%)
I find that families and friends of patients with advanced cancer encourage physical activity	1 (3%)	6 (15%)	10 (26%)	7 (18%)	8 (21%)	7 (18%)	0 (0%)
I am confident in my ability to prescribe exercise to patients with advanced cancer	1 (3%)	9 (23%)	10 (26%)	9 (23%)	3 (8%)	5 (13%)	2 (5%)
I feel that I need more information on providing physical activity recommendations to patients with advanced cancer	7 (18%)	16 (41%)	7 (18%)	6 (15%)	1 (3%)	2 (5%)	0 (0%)
I regularly consider onward referral to physiotherapy for this patient group	13 (33%)	7 (18%)	9 (23%)	4 (10%)	0 (0%)	4 (10%)	2 (5%)

Table 3 Physical activity concerns reported by physicians and associated risk factors

Concerns reported by physicians (n, %)	Associated risk factor(s) identified by physicians
Pathological fracture (26, 65%)	Presence of bone metastases Osteoporosis Androgen Deprivation Therapy Sedentary Behaviour
Spinal cord compression (14, 35%)	Vertebral Fracture Spinal Instability
Aggravation of symptom control (8, 20%) e.g. fatigue, pain	Sudden increase in physical activity levels
Musculoskeletal injury (5, 12%)	Poor manual handling techniques Concern re. heavy lifting Poor baseline activity levels

weight bearing activities" (PHY027). 5% of physicians considered onward referral to spinal surgeons and physiotherapy for further assessment.

Case study 2

All physicians, except one, stated they would be happy to recommend PA to this patient. The participant who reported they would not discuss PA with this patient stated they would like to know this patient's Mirel's score, "….might need expert ortho/physio advice re weight bearing if fracture risk high" (PHY10). The Mirels system classifies the risk of pathologic fracture based on scoring four variables on a scale of 1–3: location of lesion, radiographic appearance, size and pain. An overall score is calculated, and a recommendation for or against prophylactic fixation is made [14]. The majority of physicians mentioned the need for a multifactorial assessment of this patient prior to PA recommendation. "Current performance status and pain control plus review/knowledge of imaging would inform any recommendations (PHY012)". Physicians commented on this patient's poor baseline activity levels, "I think this gentleman will struggle to exercise…he's definitely someone that I would consider referral for an exercise programme as it would be customised to him and hopefully he may adhere to it" (PHY011). Physicians considered onward referral to orthopaedic teams and outpatient physiotherapy for advice regarding weight bearing exercise and fracture risk.

In the additional comments for this survey physicians commented on the lack of exercise prescription services available for patients living with advanced cancer "There is no mechanism to prescribe exercise in a supervised setting" (PHY07). A small number of participants mentioned a poor attitude towards prescribing exercise in Ireland "Should be encouraged, it's free and in my experience oncologists prefer to prescribe a drug, despite good quality evidence" (PHY020). "Cult of mind yourself, do nothing and take supplements as opposed to high protein diet and exercise is strong in Ireland" (PHY027).

Discussion

The results of this study demonstrate that medical and radiation oncologists and palliative care physicians consider PA important for patients with advanced cancer. Additionally, respondents believed that PA is safe for patients with advanced cancer. The majority of physicians reported that patients look to them for PA recommendations and many physicians identified a need for more information on providing PA recommendations for patients with advanced cancer.

On average, physicians responding to this survey reported discussing PA with less than half of their patient caseload. This appears similar to the number of oncology physicians discussing PA with patients in previous studies from Canada, Australia and the UK [5, 7, 15]. Cancer patients who report that their oncologist discussed exercise during treatment consultations have been shown to have higher levels of exercise during subsequent treatment [6], highlighting the benefit of discussion between physicians and patients regarding PA. A large proportion of physicians in this study were confident that patients would comply with any exercise recommendations given but were not confident in their own ability to prescribe exercise, highlighting the need for greater education around the role of exercise for patients with advanced cancer. There is a growing body of evidence detailing the benefits of aerobic and resistance exercise for patients with symptoms of advanced-stage disease, including fatigue and breathlessness [15, 16] as well as bone or visceral metastases [17, 18]. Increased educational opportunities across oncology-related specialities on the evidence provided by these studies are needed. Greater knowledge on the many benefits of exercise in this population may encourage more physicians to initiate discussions about PA with patients.

Physicians expressed many concerns regarding PA in case studies involving patients with bone metastases, centred on the risk of pathological fracture and the risk of spinal cord compression. This is a significant issue for patients with bone metastases. While consensus guidelines do not currently exist, the evidence to guide exercise prescription in this area is emerging. Individually prescribed PA programmes can be safely introduced for patients with many symptoms of advanced disease, including bone metastases [16–20]. In these studies, which describe no adverse events, all PA programmes were prescribed to reduce the loading and shear forces put on an area of metastases. The prescription of exercise by exercise specialists may be essential for safe and appropriate prescription of PA to oncology patients. If a risk of fracture is perceived as a barrier to exercise, tools to stratify risk of fracture

can be used. Mirels' classification system for impending pathologic fracture is a valid screening tool for metastatic lesions in long bones [14]. While traditionally used to identify patients in need of prophylactic fixation, this classification system could also be used to help health professionals identify patients at low risk of pathological fracture and suitable for exercise interventions.

Many physicians in this survey considered onward referral to further exercise prescription services such as supervised exercise programmes or outpatient physiotherapy; however, others commented on the lack of these services nationally. Referral to exercise specialists is not a part of the standard care received by oncology patients in Ireland. Irish cancer survivors have identified a striking lack of contact with health professionals that might be influential in facilitating recovery and rehabilitation [21]. In contrast, the American College of Surgeons Commission on Cancer produced a standard that all accredited institutions provide cancer rehabilitation services, which has spurred healthcare providers in the USA to develop cancer rehabilitation programmes across diverse delivery settings [22]. Additionally, the Institute of Medicine recommends the use of survivorship care plans that include recommendations and information regarding health promoting behaviours [23]. Despite this, the integration of rehabilitation and survivorship exercise into standard clinical cancer care continues to remain the exception rather than the norm [24]. Established clinical rehabilitation models such as cardiac rehabilitation and pulmonary rehabilitation incorporate supervised, progressive exercise training with multidisciplinary management of disease-specific side effects. These clinical models may be easily transferrable to the cancer context and provide a way to incorporate rehabilitation into the cancer care model in Ireland.

Conclusion

Overall, oncologists perceived exercise to be of benefit for patients with advanced cancer. The results of this study identify a need for physician education on providing PA recommendations for patients with advanced cancer. Concerns over the prescription of PA to patients with bone metastases highlight the need to disseminate the evidence on the benefits of PA for patients with metastatic cancer to healthcare professionals. This may encourage greater discussion between physicians and patients around PA during consultations.

Compliance with ethical standards The study protocol was approved by the Trinity College Dublin Faculty of Health Sciences Ethics Committee (Ref: 20150609).

References

1. Yee J, Davis GM, Beith JM et al (2014) Physical activity and fitness in women with metastatic breast cancer. J Cancer Surviv 8(4):647–656. https://doi.org/10.1007/s11764-014-0378-y
2. Ewald B, Attia J, McElduff P (2014) How many steps are enough? Dose-response curves for pedometer steps and multiple health markers in a community-based sample of older Australians. J Phys Act Health 11(3):509–518. https://doi.org/10.1123/jpah.2012-0091
3. Beaton R, Pagdin-Friesen W, Robertson C et al (2009) Effects of exercise intervention on persons with metastatic cancer: a systematic review. Physiother Can 61(3):141–153. https://doi.org/10.3138/physio.61.3.141
4. Albrecht TA, Taylor AG (2012) Physical activity in patients with advanced-stage cancer: a systematic review of the literature. Clin J Oncol Nurs 16(3):293–300. https://doi.org/10.1188/12.CJON.293-300
5. Jones LW, Courneya KS, Peddle C, Mackey JR (2005) Oncologists' opinions towards recommending exercise to patients with cancer: a Canadian national survey. Support Care Cancer : Off J Multinatl Assoc Support Care Cancer 13(11):929–937. https://doi.org/10.1007/s00520-005-0805-8
6. Jones LW, Courneya KS (2002) Exercise discussions during cancer treatment consultations. Cancer Pract 10(2):66–74
7. Daley AJ, Bowden SJ, Rea DW et al. (2008) What advice are oncologists and surgeons in the United Kingdom giving to breast cancer patients about physical activity? Int J Behav Nutr Phys Act 5
8. Karvinen KH, DuBose KD, Carney B, Allison RR (2010) Promotion of physical activity among oncologists in the United States. J Support Oncol 8(1):35–41
9. Martin LR, Williams SL, Haskard KB, Dimatteo MR (2005) The challenge of patient adherence. Ther Clin Risk Manag 1(3):189–199
10. Jones LW, Courneya KS, Fairey AS, Mackey JR (2004) Effects of an oncologist's recommendation to exercise on self-reported exercise behavior in newly diagnosed breast cancer survivors: a single-blind, randomized controlled trial. Ann Behav Med 28(2):105–113. https://doi.org/10.1207/s15324796abm2802_5
11. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J (2017) Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. Support Care Cancer 25:2297–2304
12. Park J-H, Oh M, Yoon YJ, Lee CW, Jones LW, Kim SI et al (2015) Characteristics of attitude and recommendation of oncologists toward exercise in South Korea: a cross sectional survey study. BMC Cancer 15:249
13. Hsieh HF, Shannon SE (2005) Three approaches to qualitative content analysis. Qual Health Res 15(9):1277–1288. https://doi.org/10.1177/1049732305276687
14. Jawad MU, Scully SP (2010) In brief: classifications in brief: Mirels' classification: metastatic disease in long bones and impending pathologic fracture. Clin Orthop Relat Res 468(10):2825–2827. https://doi.org/10.1007/s11999-010-1326-4
15. Keogh JW, Olsen A, Climstein M et al (2015) Benefits and barriers of cancer practitioners discussing physical activity with their cancer patients. J Cancer Educ. https://doi.org/10.1007/s13187-015-0893-1
16. Bourke L, Doll H, Crank H et al (2011) Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: a feasibility study. Cancer Epidemiol Biomark Prev 20(4):647–657
17. Bourke L, Gilbert S, Hooper R et al (2014) Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol 65(5):865–872
18. Cormie P, Newton RU, Spry N et al (2013) Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. Prostate Cancer Prostatic Dis 16(4):328–335

19. Oldervoll LM, Loge JH, Paltiel H et al (2006) The effect of a physical exercise program in palliative care: a phase II study. J Pain Symptom Manag 31(5):421–430
20. Oldervoll LM, Loge JH, Lydersen S et al (2011) Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 16(11):1649–1657. https://doi.org/10.1634/theoncologist.2011-0133
21. Ivers MED, Barbara A; Bates, Ursula (2009) Development, implementation and evaluation of a multidisciplinary cancer rehabilitation programme : The CANSURVIVOR Project : meeting post-treatment cancer survivors' needs
22. Surgeons ACo (2016) The commission on cancer's (CoC) cancer program standards: ensuring patient-centered care. American College of Surgeons, Chicago
23. Salz T, Oeffinger KC, McCabe MS et al (2012) Survivorship care plans in research and practice. CA Cancer J Clin 62(2):101–117. https://doi.org/10.3322/caac.20142
24. Santa Mina D, Alibhai SM, Matthew AG et al (2012) Exercise in clinical cancer care: a call to action and program development description. Curr Oncol 19(3):e136–e144. https://doi.org/10.3747/co.19.912

Appendix 7: ExPeCT Protocol Publication

Sheill *et al. Trials* (2017) 18:456
DOI 10.1186/s13063-017-2201-3

Trials

STUDY PROTOCOL Open Access

The ExPeCT (Examining Exercise, Prostate Cancer and Circulating Tumour Cells) trial: study protocol for a randomised controlled trial

Gráinne Sheill[1*†], Lauren Brady[2†], Emer Guinan[3], Brian Hayes[2,4], Orla Casey[5], John Greene[2], Tatjana Vlajnic[6], Fidelma Cahill[7], Mieke Van Hemelrijck[7], Nicola Peat[8], Sarah Rudman[7,8], Juliette Hussey[1], Moya Cunningham[5,9], Liam Grogan[5,10], Thomas Lynch[11], Rustom P. Manecksha[11], John McCaffrey[5,12], Lorelei Mucci[13], Orla Sheils[2], John O'Leary[2,14], Dearbhaile M. O'Donnell[5,15], Ray McDermott[5,16] and Stephen Finn[2,5,14]

Abstract

Background: Prostate cancer (PrCa) is the second most common cancer in Ireland. Many men present with locally advanced or metastatic cancer for whom curative surgery is inappropriate. Advanced cancer patients are encouraged to remain physically active and therefore there is a need to investigate how patients with metastatic disease tolerate physical activity programmes. Physical activity reduces levels of systemic inflammatory mediators and so an aerobic exercise intervention may represent an accessible and cost-effective means of ameliorating the pro-inflammatory effects of obesity and subsequently decrease poor cancer-specific outcomes in this patient population. This study will assess the feasibility and safety of introducing a structured aerobic exercise intervention to an advanced cancer population. This study will also examine if the evasion of immune editing by circulating tumour cells (CTCs) is an exercise-modifiable mechanism in obese men with prostate cancer.

Methods: This international multicentre prospective study will recruit men with metastatic prostate cancer. Participants will be recruited from centres in Dublin (Ireland) and London (UK). Participants will be divided into exposed and non-exposed groups based on body mass index (BMI) ≥ 25 kg/m^2 and randomised to intervention and control groups. The exercise group will undertake a regular supervised aerobic exercise programme, whereas the control group will not. Exercise intensity will be prescribed based on a target heart rate monitored by a polar heart rate monitor. Blood samples will be taken at recruitment and at 3 and 6 months to examine the primary endpoint of platelet cloaking of CTCs. Participants will complete a detailed questionnaire to assess quality of life (QoL) and other parameters at each visit.

Discussion: The overall aim of the ExPeCT trial is to examine the relationship between PrCa, exercise, obesity, and systemic inflammation, and to improve the overall QoL in men with advanced disease. Results will inform future work in this area examining biological markers of prognosis in advanced prostate cancer.

Trial registration: Clinicaltrials.gov NLM identifier: NCT02453139. Registered on 12 May 2015. This document contains excerpts from the ExPeCT trial protocol Version 1.5, 28 July 2016.

Keywords: Exercise, Advanced cancer, Metastatic, Prostate, Circulating tumour cells

* Correspondence: sheillg@tcd.ie
†Equal contributors
[1]Discipline of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin, Ireland
Full list of author information is available at the end of the article

Background

Prostate cancer

Prostate cancer (PrCa) is the most common cancer found in men in the developed world [1]. Many men present with locally advanced or metastatic cancer for whom curative surgery is inappropriate [2]. For these men, increases in progression-free and overall survival and quality of life (QoL) are the primary management objectives, and new therapies and assisting lifestyle alterations are increasingly needed.

Metabolic syndrome and prostate cancer

Obesity, known to be associated with a pro-inflammatory, pro-thrombotic humoral milieu, confers a worse prognosis in PrCa. Between 1990 and 2002, Irish male obesity increased from 8% to 20%, with a further 47% of men overweight [3]. Metabolic syndrome (MS) is a constellation of risk factors for cardiovascular disease, with central adiposity and insulin resistance being the most important components. Male hypogonadism, due to androgen deprivation therapy (ADT)—the mainstay of treatment for locally advanced and metastatic PrCa—is an independent risk factor for the various components of MS [4–8]. MS is present in 50% of all men undergoing long-term ADT [9] and is associated with progression of PrCa [10]. This may explain the excess non-cancer mortality in this population [11].

MS is characterised by low-level chronic systemic inflammation. Increasing evidence suggests that substantial cross-talk occurs between molecular pathways involved in inflammation, coagulation, and obesity [12]. Elucidation of how these pathways interact with PrCa cells may shed light on why obesity disimproves PrCa prognosis.

Circulating tumour cells and prostate cancer

Circulating tumour cells (CTCs) are identified in the blood in advanced cancer. Epithelial cells circulating in the blood of patients with carcinoma can be identified using various techniques including the ScreenCell® system (ScreenCell, Paris, France). Increasing evidence suggests that numbers of CTCs may have a prognostic role in advanced PrCa. A prospective study of castration-resistant PrCa found that ≥ 5 CTCs per 7.5 mL of blood correlated with a poor prognosis [13]. When a variety of clinical, serological, and pathological parameters were considered, the model best predictive of survival was based on baseline lactate dehydrogenase (LDH), baseline CTC count, and fold-change in CTC count at monthly intervals [14].

Natural killer cells and obesity

Natural killer (NK) cell numbers in blood and in solid organs, as well as NK cell cytotoxicity and cytokine secretion, are known to be reduced in obesity [15]. In addition, obese people with hypertension, raised fasting glucose, and an unfavourable lipid profile have less NK cells than "metabolically healthy" obese patients. Obese subjects have lower numbers of hepatic NK cells and leptin receptor-positive cells compared with those of normal weight [16]. The NK cell fraction of white blood cells is sensitive to exercise [17], and five-fold increases in NK concentrations following acute exercise have been noted. Brief exercise upregulates molecular pathways in circulating NK cells associated with cancer and cell communication [18]. In healthy young men, hypoxic exercise training leads to enhanced in-vitro NK cell cytotoxicity [19].

Interactions between platelets and circulating tumour cells

Despite the long-recognised association between cancer and thromboembolism, it has been unclear whether the thrombocytosis often seen in patients with metastases is a consequence or cause of widespread dissemination of the tumour. Accumulating evidence now shows that platelets support tumour metastasis by various mechanisms [20]. Platelets are involved in the arrest of CTCs in the vasculature and, through endothelial interactions, enable their extravasation. Platelets also secrete various pro-oncogenic factors including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), and mediate pro-survival signals in ovarian cancer cells [21].

Tumour cell-induced platelet aggregation correlates with metastatic potential, and may be due to "cloaking" of tumour cells by adherent platelets. The interaction between platelet cloaking of CTCs and tumour cell killing by NK cells is not completely understood. "Cloaking" of CTCs by adherent platelets may impede NK cell clearance of CTCs from the circulation, enhancing metastatic spread. Thrombocytopaenic mice exhibited reduced tumour metastatic burden when the tumour cells were NK cell sensitive, and in-vitro studies demonstrated reduced NK tumourilytic activity when platelets aggregated around tumour cells [22]. Platelets may enable evasion of immune editing by NK cells by conferring a "pseudonormal" phenotype on CTCs by encouraging high-level surface expression of normal major histocompatibility complex (MHC) class 1 antigen by the tumour cells [23].

In these pre-clinical studies there is an association between increased platelet-tumour cell interactions and endpoints of metastasis and death in animal models, but no clinical data exist as yet relating these interactions to outcomes in human disease. The current proposed study takes the current weight of evidence that platelet interactions are important in metastasis, and attempts to make the leap to demonstrate this in a clinical population. Platelet "cloaking" may be enhanced in obese

patients due to the pro-inflammatory, pro-thrombotic state, and may be a mechanism for worse cancer-specific outcomes in this group.

Prostate cancer and exercise

Several studies have shown that exercise may be protective against aggressive PrCa although there is no evidence that exercise protects against PrCa overall [24–27]. In PrCa patients there is solid evidence that exercise (especially group exercise) improves muscular and aerobic endurance, reduces fatigue, and improves overall quality of life [28].

Physical activity reduces levels of systemic inflammatory mediators [29], such as tumour necrosis factor (TNF)α, and so exercise may represent an accessible and cost-effective means of ameliorating the pro-inflammatory effects of obesity. This effect of physical activity depends on type, volume, and intensity, and does not depend directly on weight loss [30].

Obesity and its biochemical effects may be influenced by lifestyle changes such as exercise. As physical activity reduces levels of systemic inflammatory mediators, aerobic exercise may represent an accessible and cost-effective means of ameliorating the pro-inflammatory effects of obesity.

Methods and design

ExPeCT study objectives

The overarching hypothesis is that enhanced platelet cloaking of CTCs in obese men with prostate cancer, due to increased systemic inflammation, is a mechanism underlying worse prognosis of cancer in these patients.

The aim is to test the following four hypotheses, dividing the experimental and analytical work into four separate projects:

1. Platelet cloaking of circulating PrCa tumour cells is more prominent in men with obesity than without.
2. Regular exercise can ameliorate platelet cloaking.
3. The degree of platelet cloaking varies with levels of systemic and primary tumour inflammation and coagulability.
4. Expression of an obesity-associated lethality gene signature leads to variation in platelet cloaking.

ExPeCT study design

This international multicentre prospective study will recruit men with metastatic PrCa from five Irish hospitals and one UK hospital. This study incorporates both an observational component, with exposed and non-exposed groups defined based on body mass index (BMI), and an exercise component, with randomization to exercise and control groups for a supervised exercise programme. Participants with metastatic prostate cancer will be recruited and divided into exposed (BMI ≥ 25 kg/m^2) and non-exposed groups (BMI < 25 kg/m^2). All exposed and non-exposed participants will be randomised to an exercise group or a control group, helping to minimise bias. The exercise group will participate in a 6-month exercise programme, comprising a weekly group exercise class and a home-based exercise programme. Participants will also be encouraged to complete activity diaries. From baseline (T0) to 3 months (T3), participants in the exercise arm will meet in small groups with a chartered physiotherapist for 1 h per week. At these sessions, participants will be educated about using the Polar heart rate monitors, prescribed their target exercise intensity, and complete a half-hour group aerobic exercise class. From T3 to 6 months (T6) continued aerobic exercise will be encouraged but classes will not be supervised by a chartered physiotherapist. All patients will be offered a personal exercise advice session at the study end to discuss long-term compliance to physical activity guidelines. Any patients demonstrating a need for further follow-up in relation to their physical activity levels will be advised to attend their general practitioner (GP) for a referral to the GP exercise scheme.

The study design consists of four main projects (Fig. 1):

Project 1: CTCs will be enumerated in the T0 samples. Adherent platelets will be quantified and compared between the exposed and non-exposed groups, and correlated with clinicopathological parameters.
Project 2: The exercise group will undertake a regular supervised aerobic exercise programme, whereas the control group will not. T3 and T6 blood samples will be assessed for CTC numbers and platelet cloaking. Changes will be compared with the T0 sample, and between exposed and non-exposed, and exercise and control groups. Participants will complete a detailed questionnaire to assess QoL and other parameters at each visit.
Project 3: Blood samples will be assessed for NK cell number and activation, markers of systemic inflammation, adipokines, and serum factors related to platelet activation. The prostate needle core biopsies (NCBs) will be examined microscopically for atrophy and inflammation by morphology and immunohistochemistry, with particular reference to NK cells. All variables will be correlated with platelet cloaking.
Project 4: NCBs will be assessed for expression of an obesity-associated lethality gene signature (whose genes are known to play a role in obesity or platelet aggregation and coagulation), and correlated with platelet cloaking of CTCs.

ExPeCT participant selection criteria

Inclusion criteria

1. Written informed consent obtained before any study-related procedures.

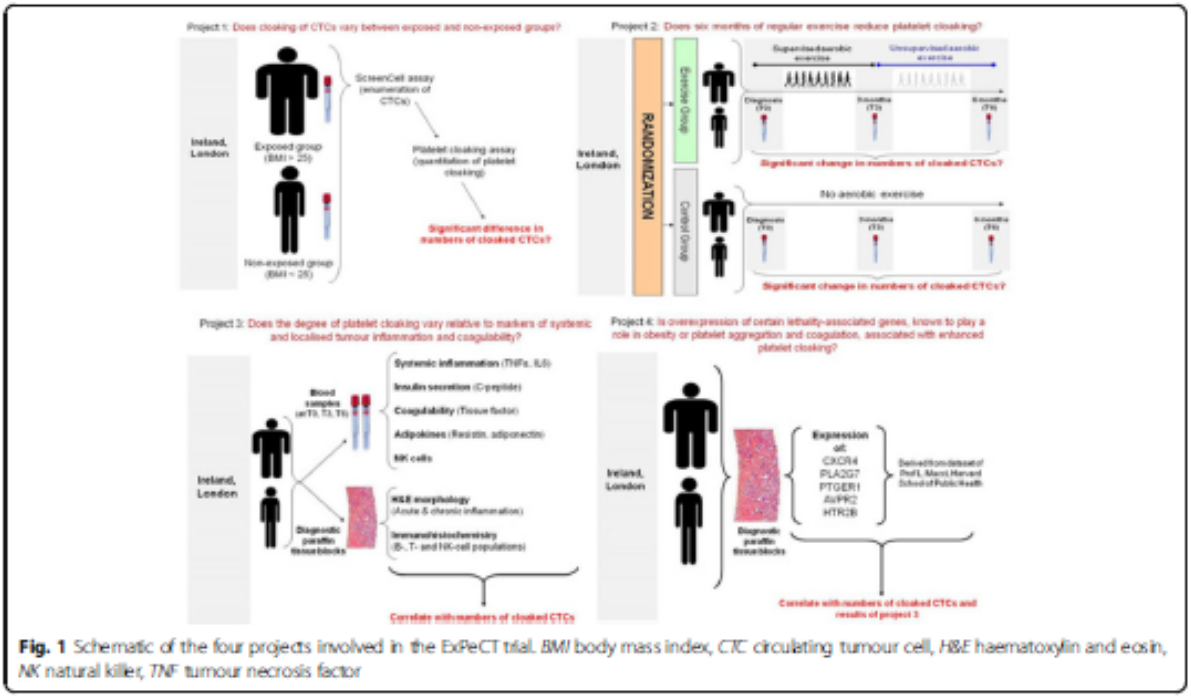


Fig. 1 Schematic of the four projects involved in the ExPeCT trial. *BMI* body mass index, *CTC* circulating tumour cell, *H&E* haematoxylin and eosin, *NK* natural killer, *TNF* tumour necrosis factor

2. Aged ≥ 18 years and male.
3. Histologically confirmed diagnosis of prostate adenocarcinoma.
4. M1 metastatic disease as confirmed by computed tomography (CT)/magnetic resonance imaging (MRI) or by bone scan, excluding patients who only have nodal metastatic disease.
5. Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to randomisation.
6. Capable of participating safely in the proposed exercise as assessed and signed off by a treating physician involved in ExPeCT recruitment.

Exclusion criteria

1. Patients with a history of radical prostatectomy.
2. Patients with other known malignancy (except non-melanoma skin cancers or fully excised carcinoma in situ at any site).

Participant enrolment procedure

Potential patients will be enrolled to the study on the basis of the inclusion/exclusion criteria. Enrolment of patients will be undertaken by staff at the medical oncology clinics at each recruiting site as well as members of the ExPeCT research team who have been delegated this task by the principle investigator (PI) (Fig. 2). Any queries about eligibility will be addressed directly to the Chief Investigator. Informed consent will be obtained by clinic staff or a member of the ExPeCT research team according to the requirements of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP).

Upon registration of new participants, a signature confirming eligibility for the trial must be obtained from a treating physician involved in ExPeCT recruitment. Each registered patient will receive a unique participant identifier number (PIN). In order to ensure random allocation of participants to each study group, the computer programme Graphpad will be used to randomly assign a treatment group to each PIN. When issuing each PIN, two gatekeepers (1 in Ireland and 1 in the UK) will inform the research team of the treatment allocation of the participant. If a participant chooses to withdraw from the study, all data obtained up to the point of withdrawal will be carried forward unless requested otherwise.

Study methodology

Demographic and clinical characteristics

A datasheet will be completed for each participant after recruitment at T0 and at the T3 and T6 follow-up visits. Data gathered will include date of birth, anthropometric parameters (body weight, standing height, waist circumference), blood pressure, routine laboratory data (serum

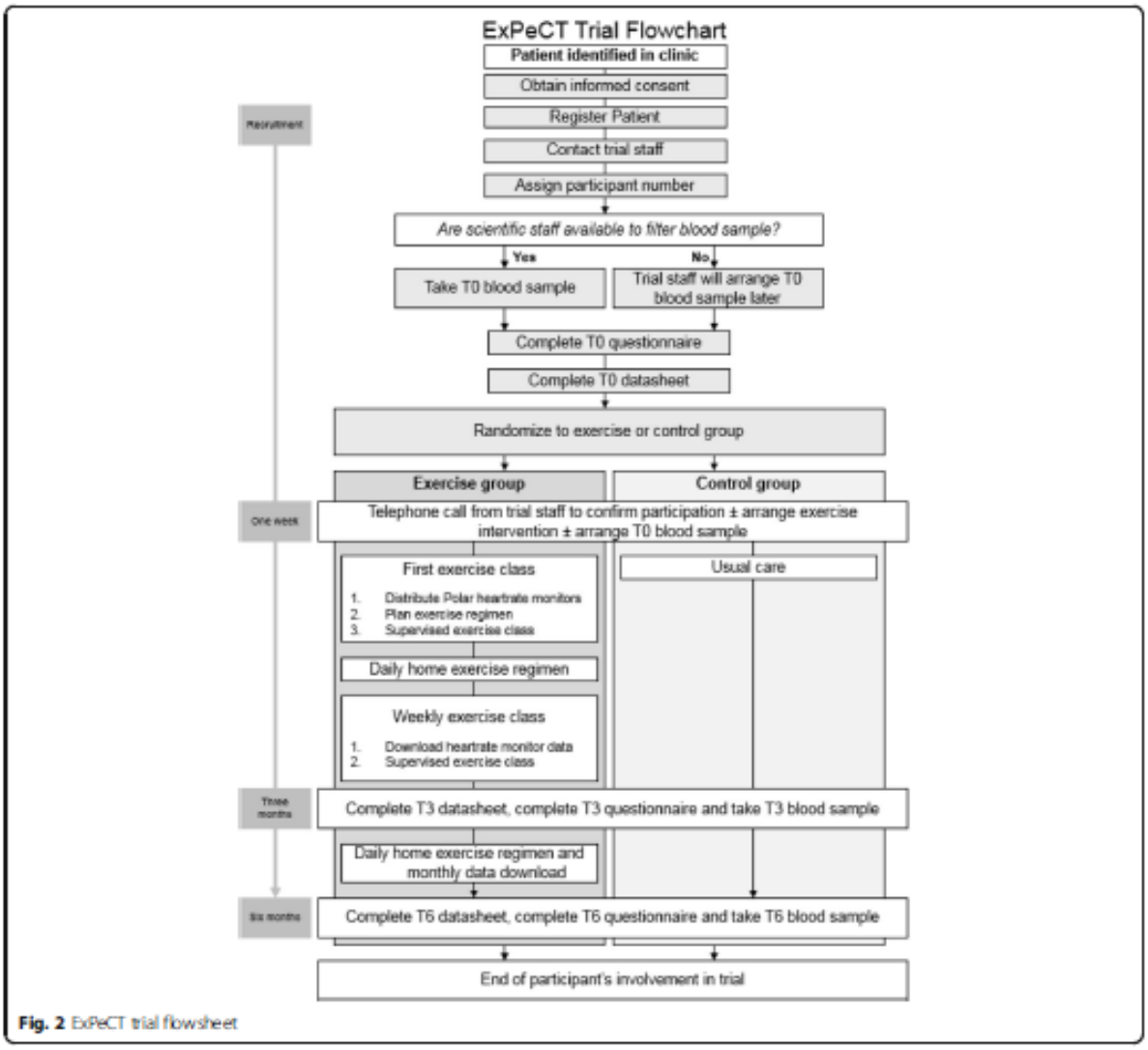


Fig. 2 ExPeCT trial flowsheet

prostate-specific antigen (PSA), haemoglobin, white cell and platelet counts), site of metastasis, and cancer-related data (stage and Gleason grade of cancer, details of current and previous systemic and radiation therapy). Data will also be recorded from three measures of physical function including balance, lower limb strength, and gait speed. These three measures will be completed with the patient by the chartered physiotherapist. Participants may also be asked to complete a structured interview session with the chartered physiotherapist exploring attitudes towards exercise. An overview of all data collected is included in Fig. 3.

Primary study endpoint

Platelet cloaking of circulating tumour cells

For each clinical review episode (at baseline and after 3 and 6 months), 12–16 mL of blood drawn from each patient into K_2-EDTA tubes will be filtered by a ScreenCell® Cyto kit within 4 h. CTC enrichment depends on vacuum-assisted filtration through a microporous membrane filter to separate CTCs from other blood cells on the basis of size. Three to five filters will be generated for each participant, two of which will be stained with May-Grunwald Giemsa, followed by a broad-spectrum epithelial marker, and one to three reserved for platelet cloaking assays and other relevant markers. CTCs will be enumerated cytologically. The degree of platelet adhesion to CTCs will be assessed by immunohistochemistry. The number of CTCs with adherent platelets will be counted, and the approximate number of platelets adherent to each cell will be estimated.

			Study Period			
			Enrolment	T0	T3	T6
		Eligibility Screen	X			
		Informed Consent	X			
		Allocation	X			
Type of Data	Details Collected	Instrument Used				
Demographic and Clinical Measures	Background Details (age at diagnosis, domiciliary situation, comorbidities, recent medications)	Physicians' Health Study Assessment		X	X	X
	Blood Pressure, BMI, Waist Circ.	Clinical Registration Form		X	X	X
Subjective Lifestyle Measures	Stress	Perceived Stress Scale – 4		X	X	X
	Memory and Cognition	Physicians' Health Study Assessment		X	X	X
	Pain	Brief Pain Inventory Scale		X	X	X
	Smoking and Alcohol	Physicians' Health Study Assessment		X	X	X
	Physical Activity	Physicians' Health Study Assessment		X	X	X
	Depression	PHQ-9		X	X	X
	Diet (dairy products, meat, vitamin D)	Physicians' Health Study Assessment		X	X	X
	Quality of Life	FACT-P		X	X	X
	Sleep	Pittsburgh Sleep Quality Index		X	X	X
Physical Function Measures	Physical Activity Measurements	Actigraph Accelerometers		X		
	Physical Performance Measurements	Short Physical Performance Battery		X	X	X
	Adherence to Exercise Programme	FT7 Polar Monitors, Patient Exercise Diaries		X	X	X
Biological Measures	Circulating Tumour Cells	ScreenCell® system		X	X	X
	Serum and Plasma	Vacuette® system		X	X	X
	Natural Killer Cells[a]	Vacuette® system		X	X	X
	Diagnostic Paraffin Tissue Blocks	Original diagnostic NCB paraffin tissue blocks	X			

Fig. 3 ExPeCT SPIRIT figure. [a]Natural killer cell testing will only be performed at Irish sites. *BMI* body mass index, *Circ.* Circumference, *FACT-P* Functional Assessment of Cancer Therapy scales for Men with Prostate Cancer, *NCB* needle core biopsy, *PHQ* Patient Health Questionnaire

Secondary study endpoints

Systemic and localized tumour inflammation and coagulability

This part of the project consists of measurement of systemic and prostate inflammation, markers of coagulation, cytokines, and NK cells. The substrates for this work will be blood samples taken from each participant at T0, T3, and T6, and the original diagnostic NCB paraffin tissue blocks. Examples of the serological and haematological tests include adiponectin, leptin, and resistin.

Expression of lethality-associated genes

This project will evaluate expression of selected genes known to be associated with PrCa progression, coagulation, and stem cell-like phenotype in diagnostic NCBs. Sections of formalin-fixed, paraffin-embedded tissue blocks will be cut from each patient's diagnostic prostate NCB specimen. These sections will be dissected by either laser capture microdissection or gross dissection. Ribonucleic acid (RNA) will be extracted from the microdissected tissue. Gene expression profiling will be undertaken on diagnostic biopsy material using custom-designed assays designed to detect only mRNA and to traverse the exonic junction. Assays for the genes CXCR4, PLA2G7, PTGER1, AVPR2, and HTR2B will be employed. Quantitation of results of polymerase chain reaction (PCR) will be undertaken using the ΔΔCt method, comparing the Ct values of the samples of interest with a control or calibrator such as a non-treated sample or RNA from normal tissue. Diagnostic material may be used for further gene expression analysis associated with obesity as part of the trial.

Quality of life assessment

All participants will complete a detailed questionnaire after recruitment at T0, and again at T3 and T6. The sections of the questionnaire are as follows:

1. Background details (age at diagnosis, domiciliary situation, comorbidities, recent medications).

2. Smoking and alcohol.
3. Sleep (Pittsburgh Sleep Quality Index [31]).
4. Stress (Perceived Stress Scale – 4).
5. Depression (Patient Health Questionnaire (PHQ)-9) [32].
6. Quality of life (FACT-P) [33].
7. Memory and cognition.
8. Physical activity.
9. Diet (dairy products, meat, vitamin D).
10. Pain (Brief Pain Inventory Scale) [34].

Some sections of the questionnaire are stand-alone validated instruments (such as the Functional Assessment of Cancer Therapy scales for Men with Prostate Cancer (FACT-P), which is designed to assess health-related quality of life in this setting [33]). Others, such as the sections on physical activity and diet, are derived from a prostate cancer-specific questionnaire used in the large Physicians' Health Study based at Harvard University [35].

Exercise programme

The exercise group will participate in a 6-month moderate-to-vigorous intensity aerobic exercise programme comprising a weekly class and a home-based aerobic exercise programme. Participants will also be encouraged to complete weekly activity diaries. From T0 to T3, participants in the exercise arm will meet in small groups with a chartered physiotherapist for 1 h per week. During the first class the participants will receive an introduction to the format of the exercise and will be educated on safe exercise practices and strategies to monitor exercise exertion.

Each exercise participant will receive, and be educated about using, a Polar heart rate monitor for the duration of the study. Participants will exercise to a prescribed heart rate range during class and home sessions. Exercise prescription will progress in intensity and duration during months 1 and 2 of the programme to reach the target 3 h per week (180 min/week) of moderate-to-vigorous intensity activity from month 3 onwards (Table 1). This level of activity has been previously shown to be associated with a 33% reduction in all-cause mortality following prostate cancer [36]. Participants will be encouraged to achieve this target exercise in six 30-min sessions throughout the week. However, flexibility will be allowed to facilitate longer or shorter session to a total of 180 min/week. Each exercise session must be of at least 10 min duration. The research team has previously shown that similar aerobic activity intensities can be achieved in cancer survivors through a home-based walking programme and that a Polar heart rate monitor was an acceptable means of monitoring activity intensity [37].

During months 1–3, data from the Polar heart rate monitor will be downloaded weekly to monitor adherence. Participants will be scheduled to attend the research centre once monthly from T3 to T6 to download data and encourage ongoing adherence to the programme. In addition, participants will receive weekly telephone contact from the ExPeCT research team from T3 to T6 to encourage adherence.

The control group will not be given specific advice regarding exercise beyond that considered usual medical care, and will not be invited to participate in the aerobic exercise group. Participants will be reviewed at T3 and T6 following the baseline visit and anthropometric measurements and further blood samples taken. Participants assigned to the control group will be offered a personal exercise advice session following completion of the T6 assessment.

Table 1 Exercise intensity during supervised classes

Supervised exercise classes		Exercise intensity (% heart rate reserve) by baseline fitness group			Duration
		Poor	Fair	Average	(min)
Month 1	Week 1	40–50%	50–60%	55–65%	20
	Week 2	40–50%	50–60%	55–65%	20
	Week 3	45–55%	55–65%	60–70%	20
	Week 4	45–55%	55–65%	60–70%	30
Month 2	Week 5	50–60%	60–70%	65–75%	30
	Week 6	50–60%	60–70%	65–75%	30
	Week 7	55–65%	65–75%	65–75%	30
	Week 8	55–65%	65–75%	65–75%	30
Month 3	Week 9	60–70%	65–75%	65–75%	30
	Week 10	60–70%	65–75%	65–75%	30
	Week 11	60–75%	65–75%	65–75%	30
	Week 12	60–75%	65–75%	65–75%	30

Exercise prescription

Participants will be asked to self-rate their baseline activity levels as one of three categories as per American College of Sports Medicine (ACSM) guidelines:

1) Sedentary or minimally active, not completing any moderate to vigorous activity (equivalent to poor fitness levels).
2) Sporadic physical activity, suboptimal exercise (equivalent to fair fitness levels).
3) Habitual physical activity, regular moderate to vigorous exercise (equivalent to average fitness levels).

Exercise intensity will be prescribed using individualised heart rate reserve (HRR) ranges in accordance with the ACSM guidelines. The following formula will be used to calculate HRR and heart rate (HR) range prescriptions: (target % × [maximum HR − resting HR] + resting HR). For each participant, age-predicted maximal HR will be calculated using the following equation: (206.9 − [0.67 × age]) [38]. Participants with self-rated 'poor' fitness levels (category 1) will commence the programme at an aerobic intensity of 40–50% HRR. Those with self-rated 'fair' fitness levels (category 2) will commence the programme at an aerobic intensity of 50–60% HRR, and those with self-rated 'average' fitness levels (category 3) will commence the programme at 55–65% HRR. The duration and frequency of the home exercise programme sessions is outlined in Table 2.

Patients will also be encouraged to use the Borg Breathlessness Scale. Using this scale, participants will give a subjective rating of perceived exertion. It is a widely used and reliable indicator to monitor and guide exercise intensity [39]. The scale allows individuals to subjectively rate their level of exertion during exercise and can be used to correlate exertion levels with exercise heart rates [40]. The Borg scale will be particularly valuable with participants on beta blockers as measures of exercise intensity are inaccurate or dampened on these medications and polar monitors may not reflect an accurate heart rate during exercise.

Forms of aerobic exercise undertaken at the supervised exercise classes will specifically avoid activities which may be associated with higher risk (e.g. the use of rowing machines in participants with lumbar spinal metastases). Walking on treadmills is a low-risk exercise activity.

Exercise follow-up

Participants will be invited to attend outpatient departments 6 months after T0 and the trial datasheet, questionnaire, and physical function measures will again be completed. Blood samples will be obtained in the same fashion as for the T0 visit. All patients will be offered a personal exercise advice session at study end to discuss long-term compliance to physical activity guidelines. Any patients demonstrating a need for further follow-up in relation to their physical activity levels will be advised to attend their GP for a referral to the GP exercise scheme. After this visit, participants will be thanked for their involvement and discharged from the study.

Table 2 Home-based exercise intensity

Home-based walking programme		Exercise intensity (% heart rate reserve) by baseline fitness group			Time	
		Poor	Fair	Average	Days/week	Duration (min)
Month 1	Week 1	40–50%	50–60%	55–65%	2	20
	Week 2	40–50%	50–60%	55–65%	3	20
	Week 3	45–55%	55–65%	60–70%	3	20
	Week 4	45–55%	55–65%	60–70%	3	30
Month 2	Week 5	50–60%	60–70%	65–75%	3	30
	Week 6	50–60%	60–70%	65–75%	4	30
	Week 7	55–65%	65–75%	65–75%	4	30
	Week 8	55–65%	65–75%	65–75%	5	30
Month 3	Week 9	60–70%	65–75%	65–75%	5	30
	Week 10	60–70%	65–75%	65–75%	5	30
	Week 11	60–75%	65–75%	65–75%	5	30
	Week 12	60–75%	65–75%	65–75%	5	30
Month 4	Weeks 13–16	60–75%	65–75%	65–75%	6	30
Month 5	Weeks 17–20	60–75%	65–75%	65–75%	6	30
Month 6	Weeks 12–24	60–75%	65–75%	65–75%	6	30

Study duration

The study is scheduled to last for 4 years; initial funding was drawn down in April 2014. Enrolment commenced in November 2014 and closed in May 2017 in order to allow enrolled participants to complete their 6 months of follow-up and exercise programme and for all laboratory work and analysis to be finished before the study completion date.

Patient withdrawal and off-study procedure

Patients are free to withdraw from participation in the study at any time upon request. An off-study form must be completed and sent to the ExPeCT research team if a patient withdraws from the study or leaves due to another reason (e.g. study completion, extraordinary medical circumstances, lost to follow-up).

Incident reporting

The occurrence and severity of any incidents from the time of consent to completion of the programme at 6 months will be recorded by the chartered physiotherapist on a standardised reporting form (e.g. adverse events occurring as a result of exercise or adverse reactions to study blood draws). All incidents will be reported to the site PI. Incidents will be followed until resolution or until a patient withdraws from the study or leaves due to another reason (e.g. study completion, extraordinary medical circumstances, lost to follow-up). Recurrent incidents in the same patient will be counted as separate incidents.

Data management

The ExPeCT research team will be the only people with access to the data collected in the course of this project. Data analysis will be performed at St. James's Hospital by the in-house bioinformatics team and other members of the ExPeCT research team. At the end of the study period, when all analysis is complete, data will be retained by the ExPeCT research team. Data will be securely stored for up to 10 years with the option of requesting ethical permission for a prolonged storage time.

Sample size

We will recruit 200 participants over the lifetime of the study, evenly divided between the exercise group and the control group. To calculate the power of the study, we used data from a previous study of ovarian cancer cell lines which showed approximately 2% platelet adhesion [21]. A standard deviation (SD) varying from 2% to 10% would enable us to detect a difference of platelet cloaking of between 0.79% and 3.9%. Research into this area is at an early stage and the clinical importance of specific incremental changes in the degree of platelet cloaking is as yet uncertain, but its elucidation is beyond the scope of this study.

With regard to the detection of changes in platelet cloaking with time, and taking the same assumptions regarding SD of platelet adhesion in PrCa CTCs as in project 1, we will be able to detect a change of 1.8% platelet cloaking between any two time points in the 100 participants in each of the exercise and the control groups, determined by paired t testing. A SD varying from 2% to 10% would enable us to detect a difference of platelet cloaking of between 0.56% and 2.8%. Generalised linear mixed models will be employed in order to account for the correlation between multiple measurements in the same experimental subject.

Statistical analysis

Project 1 will compare the number of cloaked platelets, comparing healthy weight and overweight men using either the t test or the non-parametric Mann-Whitney test, depending on the normality of the data. Linear regression models will be used to test the association between obesity and extent of platelet cloaking, adjusting for potential confounders such as age, use of medications, and smoking. If the data are not normally distributed then a log transformation will be employed. In addition to comparing overweight and healthy weight men as a binary exposure, BMI will be modelled as an ordinal variable (<18.5, 18.5–24.9, 25.0–27.4, 27.5–29.9, 30+) and as a continuous variable and to test for linear trends with the log likelihood ratio test of nested models.

Project 2 will compare measurements of platelet cloaking at baseline and months 3 and 6 follow-up time points among men randomised to the exercise and control arms, in both the exposed (BMI ≥ 25) and non-exposed (BMI < 25) groups. Intention-to-treat analyses will use linear mixed-effect models to incorporate each biomarker for a given participant over time. BMI will also be stratified to look at potential effect modification. To estimate longitudinal changes in quality of life scores from baseline, the primary analysis will be carried out using a mixed-effects model for repeated measures.

Project 3 will examine the extent of the inflammatory infiltrate in diagnostic NCBs. All variables will be correlated with CTC numbers and platelet cloaking using basic descriptive statistics such as Pearson correlation coefficients for continuous variables and simple t tests for categorical variables. In the event of skewed distributions or sparse data, we will use non-parametric tests such as the Spearman correlation and Mann-Whitney. Moreover, a principal component analysis will be undertaken to estimate the proportion of variability in platelet cloaking and CTC number which is explained as a function of the obesity inflammatory biomarkers. The biomarkers will be modelled as principal components in the

linear regression and adjusted for potential confounders such as age, smoking, and other factors.

Project 4: Generalized linear regression models will be used to examine whether obesity is associated with expression of each of the five markers in the tumour tissue, adjusting for potential confounders such as age and smoking status, as well as clinical features. Obesity will be dichotomised as BMI greater or less than 25, and we will also model BMI as a continuous variable and examine tests for trend. The expression of each marker will be assessed with respect to the extent of platelet cloaking (high, intermediate, and low). The categorisation of platelet cloaking as high, intermediate, and low is dependent on the proportion of CTCs with adherent platelets (high > 75%, intermediate 25–75%, low < 25%). A gene score will be created by ranking individuals across expression of each gene in tertiles, assigning points for each marker as lowest tertile = 0, middle tertile = 1, upper tertile = 2, and calculating a summary score.

Ethics and research governance

The study protocol and other documentation have been approved by NRES Committee London—Camden & Islington (REC reference 14/LO/1859), The Mater Misericordia Hospital Research Ethics Committee, Dublin (REC reference: 1/378/1760), Beaumont Hospital Ethics (Medical Research) Committee, Dublin (REC Reference 15/73), SJH/AMNCH Research Ethics Committee, Dublin (REC Reference: 2014-11 List 41 (6)) and St Luke's Radiation Oncology Network, Dublin (REC Number not assigned. Trial referred to as ICORG 15-21 (sponsorship identifier)).

Cancer Trials Ireland is the sponsor for the Irish sites on this study (Protocol Number CTRIAL-IE (ICORG) 15-21).

Discussion

Many patients diagnosed with PrCa are not suitable for radical therapy because of the extent or grade of disease. In those patients who have potentially curable disease, obesity and its complications may make radical surgery impractical. ADT is itself a cause of obesity and metabolic syndrome. For all of these reasons, men with PrCa who are obese are less likely to be treated with curative intent. Medical therapy is improving for the cardiovascular complications of obesity which are the major competing cause of death in these men. As control of obesity-related cardiovascular risk factors improves, aggressiveness of PrCa becomes more important in determining the cause of mortality. It is known that obese men have a worse outlook regarding cancer-related mortality than non-obese men. The combination of an ageing population with an increased PrCa incidence, increasing obesity prevalence, and improved management of cardiovascular risk factors means that in the future, simply put, more men are going to die as a result of the deleterious effect of being overweight in advanced PrCa. Demonstration that platelet cloaking is a mechanism by which obesity disimproves PrCa survival would suggest that therapies targeted at points along the pathway of platelet activation could be efficacious. For example, adiponectin supplementation or blockade of interleukin (IL)-6 or TNFα could be useful. Comparison of the expression of lethality-associated genes between the primary site and CTCs could highlight genes which are upregulated as part of the metastatic pathway, with potential for targeted therapy.

ExPeCT aims to elucidate a potential mechanism by which obesity confers a worse prognosis in PrCa, two increasingly prevalent diseases in the Western world. ExPeCT hopes to show that a low-cost, accessible exercise programme can improve QoL and potentially ameliorate the effects of obesity through alterations in the systemic adipokine and inflammatory mediator profile.

Trial status

ExPeCT trial protocol Version 1.5, 28 July 2016. Recruitment was initiated in October 2014 and continued until May 2017. Data collection is ongoing for enrolled participants and is expected to conclude in November 2017.

Abbreviations

ACSM: American College of Sports Medicine; ADT: Androgen deprivation therapy; BMI: Body mass index; CT: Computed tomography; CTC: Circulating tumour cell; FACT-P: Functional Assessment of Cancer Therapy scales for Men with Prostate Cancer; GP: General practitioner; HR: Heart rate; HRR: Heart rate reserve; ICH-GCP: International Conference on Harmonisation-Good Clinical Practice; IL: Interleukin; K_2-EDTA: Ethylenediaminetetraacetic acid; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; MS: Metabolic syndrome; NCB: Needle core biopsy; NK: Natural killer; PCR: Polymerase chain reaction; PDGF: Platelet-derived growth factor; PHQ: Patient Health Questionnaire; PI: Principal Investigator; PIN: Participant identifier number; PrCa: Prostate cancer; PSA: Prostate-specific antigen; QoL: Quality of life; RNA: Ribonucleic acid; SD: Standard deviation; T0: Baseline; T3: Three months; T6: Six months; TNF: Tumour necrosis factor; VEGF: Vascular endothelial growth factor

Acknowledgements

The authors would like to acknowledge their partnership with the Transdisciplinary Prostate Cancer Partnership (ToPCaP; www.topcapteam.org).

Funding

The ExPeCT trial is funded by the World Cancer Research Fund, grant reference number: 2013/1003.

Availability of data and materials

Not applicable to this study.

Authors' contributions

All authors have read and approved the final manuscript. SF, DMOD, RMD, JH, BH, and JOL are co-applicants on the initial grant proposal. BH and EG contributed to the original grant proposal and protocol. GS and LB contributed to the production of this manuscript and to protocol development. OC contributed to study coordination.

Ethics approval and consent to participate
The study protocol and other documentation have been approved by NRES Committee London—Camden & Islington (REC reference 14/LO/1859), The Mater Misericordia Hospital Research Ethics Committee, Dublin (REC reference: 1/378/1760), Beaumont Hospital Ethics (Medical Research) Committee, Dublin (REC Reference 15/73), SIH/AMNCH Research Ethics Committee, Dublin (REC Reference: 2014-11 List 41 (6)) and St Luke's Radiation Oncology Network, Dublin (REC Number not assigned. Trial referred to as ICORG 15-21 (sponsorship identifier)). Written informed consent will be obtained from each participant before any study-related procedures.

Consent for publication
Not applicable to this study.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details
[1]Discipline of Physiotherapy, School of Medicine, Trinity College Dublin, Dublin, Ireland. [2]Department of Histopathology and Morbid Anatomy, Trinity Translational Medicine Institute, Dublin, Ireland. [3]School of Medicine, Trinity College Dublin, Dublin, Ireland. [4]Department of Histopathology, Cork University Hospital, Wilton, Cork, Ireland. [5]Cancer Trials Ireland, Dublin, Ireland. [6]Institute of Pathology, University Hospital Basel, Basel, Switzerland. [7]King's College London, School of Cancer and Pharmaceutical Sciences, Translational Oncology & Urology Research (TOUR) , London, UK. [8]Guy's and St Thomas' NHS Foundation Trust, London, UK. [9]Department of Radiation Oncology, St Luke's Hospital, Dublin, Ireland. [10]Department of Oncology, Beaumont Hospital, Dublin, Ireland. [11]Department of Urology, St James's Hospital, Dublin, Ireland. [12]Department of Oncology, Mater Misericordiae, Dublin, Ireland. [13]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA. [14]Department of Histopathology, St James's Hospital, Dublin, Ireland. [15]HOPE Directorate, St James's Hospital, Dublin, Ireland. [16]Department of Oncology, Adelaide and Meath Hospital incorporating the National Children's Hospital, Dublin, Ireland.

Received: 29 March 2017 Accepted: 6 September 2017
Published online: 04 October 2017

References

1. Ferlay J, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–917.
2. Jani AB. Management strategies for locally advanced prostate cancer. Drugs Aging. 2006;23(2):119–29.
3. McCarthy SN, Gibney MJ, Flynn A. Overweight, obesity and physical activity levels in Irish adults: evidence from the North/South Ireland food consumption survey. Proc Nutr Soc. 2002;61(1):3–7.
4. Smith JC, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab. 2001;86(9):4261–7.
5. Dockery F, et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond). 2003;104(2):195–201.
6. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006;91(4):1305–8.
7. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448–56.
8. Keating NL, et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1):39–46.
9. Braga-Basaria M, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006;24(24):3979–83.
10. Smith MR, et al. Diabetes and mortality in men with locally advanced prostate cancer: RTOG 92-02. J Clin Oncol. 2008;26(26):4333–9.
11. Van Hemelrijck M, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the population-based PCBaSe Sweden. J Clin Oncol. 2010;28(21):3448–56.
12. Zhang N, Lawrence DA. Tissue factor and obesity, a two-way street. Nat Med. 2011;17(11):1343–4.
13. de Bono JS, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res. 2008;14(19):6302–9.
14. Scher HI, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol. 2009;10(3):233–9.
15. Lynch LA, et al. Are natural killer cells protecting the metabolically healthy obese patient? Obesity (Silver Spring). 2009;17(3):601–5.
16. Lautenbach A, et al. Human obesity reduces the number of hepatic leptin receptor (ob-R) expressing NK cells. Endocr Res. 2011;36(4):158–66.
17. Timmons BW, Cieslak T. Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev. 2008;14:8–23.
18. Radom-Aizik S, et al. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. J Appl Physiol (1985). 2013;114(5):628–36.
19. Wang JS, Weng TP. Hypoxic exercise training promotes antitumour cytotoxicity of natural killer cells in young men. Clin Sci (Lond). 2011;121(8):343–53.
20. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011;11(2):123–34.
21. Egan K, et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. PLoS One. 2011;6(10):e26125.
22. Nieswandt B, et al. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. Cancer Res. 1999;59(6):1295–300.
23. Placke T, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. Cancer Res. 2012;72(2):440–8.
24. Giovannucci EL, et al. A prospective study of physical activity and incident and fatal prostate cancer. Arch Intern Med. 2005;165(9):1005–10.
25. Patel AV, et al. Recreational physical activity and risk of prostate cancer in a large cohort of US men. Cancer Epidemiol Biomarkers Prev. 2005;14(1):275–9.
26. Nilsen TI, Romundstad PR, Vatten LJ. Recreational physical activity and risk of prostate cancer: a prospective population-based study in Norway (the HUNT study). Int J Cancer. 2006;119(12):2943–7.
27. Johnsen NF, et al. Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Int J Cancer. 2009;125(4):902–8.
28. Keogh JW, MacLeod RD. Body composition, physical fitness, functional performance, quality of life, and fatigue benefits of exercise for prostate cancer patients: a systematic review. J Pain Symptom Manage. 2012;43(1):96–110.
29. Ho SS, et al. Effects of chronic exercise training on inflammatory markers in Australian overweight and obese individuals in a randomized controlled trial. Inflammation. 2013;36(3):625–32.
30. Balducci S, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis. 2010;20(8):608–17.
31. Buysse DJ, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213.
32. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13.
33. Esper P, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997;50(6):920–8.
34. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129–38.
35. Deo P, Nayak R, Rajpura J. Women's attitudes and health beliefs toward osteoporosis screening in a community pharmacy. J Osteoporos. 2013;2013:650136.
36. Kenfield SA, et al. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011;29(6):726–32.
37. Broderick JM, et al. Feasibility and efficacy of a supervised exercise intervention in de-conditioned cancer survivors during the early survivorship phase the PEACH trial. J Cancer Surviv. 2013;7(4):551–62.

38. Kohl HW, et al. An empirical evaluation of the ACSM guidelines for exercise testing. Med Sci Sports Exerc. 1990;22(4):533–9.
39. Wilson RC, Jones PW. Long-term reproducibility of Borg scale estimates of breathlessness during exercise. Clin Sci (Lond). 1991;80(4):309–12.
40. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.

Appendix 8: ExPeCT Training Record

Study Training Record

ICORG Study Nº.:	**15-21**
Study Short Name :	**The ExPeCT Trial**
Study Title:	**The ExPeCT Trial (Exercise, Prostate and Circulating Tumour cells)**
Current Protocol Version/ Date:	**Version 1.5 / 28th -July-2016**
Trainee Name:	
Job Title:	

TOPIC *(Compulsory by All (•), Optional for PI (□))*	
• Study Status • Study Background • Objectives • Study Design • Inclusion/Exclusion Criteria • Informed consent • Study parameters Recruitment SJH • Patient Referral • Use of Information and Publication of Findings • Indemnity/Monitoring/Audit/GCP ☐ Sample Collection ☐ Labelling ☐ ExPeCT scientists, contact details ☐ CRFs/Sample Log ☐ Questions/Paperwork ☐ Contacts	
Date Training Received	
Trainee Signature	
Trainer Name	
Trainer Signature	
Date	

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Appendix 9: Sample ExPeCT Patient Information Leaflet

ExPeCT Trial (Exercise, Prostate cancer and Circulating Tumour cells)

Patient Information Leaflet

Site Doctor/Principal Investigator:	Prof John McCaffrey
Study Doctor Address:	Mater Misericordiae University Hospital, Dublin 7
ICORG Study Number:	ICORG 15-21
Name of Institution leading the research:	Trinity College Dublin
Chief Investigator's Name:	Prof Stephen Finn

Sponsor/Supporter Name and Address: ICORG – the All Ireland Cooperative Oncology Research Group (ICORG), 60 Fitzwilliam Square North, Dublin 2, Ireland.

Introduction:

You are being invited to take part in a research study taking place in St. James's Hospital, Dublin 8. Before you decide whether or not you wish to take part, you should carefully read the information provided below, and if you wish, discuss this with your family, friends or GP. Please take time to ask questions. Do not feel rushed or under any obligation to decide quickly. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you. This process is known as Informed Consent.

Why is this study being done?

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

The human body, including the prostate gland, is made up of billions of tiny cells. Sometimes a small number of these cells start to grow too rapidly and become cancer cells. In men with metastatic prostate cancer, these cancer cells can spread beyond the prostate gland and can be found floating in the blood, where they are called “circulating tumour cells” (CTCs). Very small blood particles (called platelets) become stuck to these CTCs, an occurrence which is called “platelet cloaking”. Platelet cloaking may prevent the body’s defence systems from recognising and killing the cancer cells and allowing them to spread around the body.

Men who are overweight are more likely to develop blood clots, because their platelets are stickier than in men of normal weight. Exercise can improve quality of life for men with cancer and can reduce the stickiness of platelets; therefore, we anticipate that exercise might result in reduced platelet cloaking and, therefore help to reduce or even prevent the spread of cancer cells in overweight men.

This study aims to investigate this by measuring platelet cloaking of CTCs in overweight and normal-weight men with prostate cancer, and the effect of exercise on platelet cloaking and other markers, such as protein or DNA, in the blood which are associated with platelet cloaking.

Who is organising and funding this study?

This study has been organised by Prof Stephen Finn and researchers in Trinity College Dublin in collaboration with the Irish Clinical Oncology Research Group (ICORG). The project is funded by the World Cancer Research Fund, a global network of charities which fund research into the links between cancer, diet, exercise and other lifestyle factors.

What will happen to me if I agree to take part?

If you decide to join the study you will be asked**:**

1. To travel to St. James’s Hospital to provide a blood sample on three occasions, each three months apart. Less than 2 tablespoons of blood will be drawn on each occasion.

   These blood samples will be taken by a member of the research team in the Clinical Research Facility in St. James’s Hospital in Dublin. The research laboratory will then analyse the blood sample for key elements such as proteins,

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

DNA, CTCs and platelet cloaking. Your doctor will not be informed about any results and your treatment will not be affected by this study.

2. To complete a questionnaire at each occasion of blood draw while in St. James's Hospital.

This will gather information regarding your quality of life, your diet, how well you are sleeping, any medications you take and your psychological well-being. Cancer is a disease which touches every aspect of a man's life, which should be captured through the questionnaire. The questionnaire will take approximately 60 minutes to complete. The total time for each appointment will be 90 minutes.

3. This study is a randomized study. This means that, if you agree to join the study, a random decision will be made as to whether or not you will be also asked to participate in an exercise programme (see paragraph 4 below).

Before you agree to join the study, neither the doctors, who are treating you, nor the researchers conducting the study will know whether you will be randomized to participate in this exercise programme or be part of the control group. It is, therefore, important for you to decide whether or not you would be happy to participate in the exercise programme before you agree to join the study.

4. If you are randomised to take part in the exercise programme you will be asked to participate in a regular exercise programme. This will involve a weekly one-hour class with a physiotherapist and several other men with prostate cancer in the Clinical Research Facility in St. James's Hospital. This part of the exercise programme will last for three months.

You do not need to be someone who already takes regular exercise in order to be able to participate – the programme is suitable for all fitness levels and will be tailored to your abilities. The exercise programme will focus on aerobic exercise, eg. Walking, running, cycling. If you are asked to participate in the exercise programme you will also be given a small machine to measure your heartrate, and encouraged to do some exercise every day. After completing a three months program you will no longer have a weekly exercise class, and will be encouraged to continue exercising every day.

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

5. If you do agree to join the study, some of your medical details will also be collected by the researchers, and your height, weight and waist circumference will be recorded at each three monthly check-up.

6. In addition, the tissue from your prostate biopsy which provided your original diagnosis of prostate cancer will be retrieved from the laboratory in the Mater Hospital and analysed by the research team in St. James's Hospital as part of the research.

Who and how many people will take part in the study?

Men with prostate cancer who are known to have metastatic disease will be invited to take part. We will invite about 200 patients to take part in this study, 133 from Ireland and 67 from London.

How long will I be on the study?

Your total involvement in the study would be 6 months.

Do I have to take part?

You do not have to take part in this study and if you decide not to take part, it will have no effect on your care now or in the future.

Can I stop being on this study?

If you do decide to take part, you can change your mind at any time without having to give a reason and without any effect on the care you will receive from the medical staff.

Can anyone else stop me from being in this study?

The study doctor or physiotherapist may stop you from taking part in our research at any time if:

- It is in your best interest.
- You do not follow your study responsibilities.

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

- You do not meet the study criteria.
- The study is stopped by the sponsor.

What are the possible benefits of taking part?

If you take part in the study and agree to give samples, you may help scientists and doctors understand the significance of circulating tumour cells in the blood. This may improve treatment for cancer patients in the future.
It is important for you to realise that the research study is designed to increase knowledge and understanding of cancer, and so you yourself will not benefit from taking part in it. However, if you are asked to participate in the exercise programme, you may benefit from the experience of taking regular exercise. For some men, this may help to improve symptoms, sleep and general quality of life, as well as improving your general health.
Please note that your doctors will not be informed of the results. Your doctors will make decisions about your treatment independent from this study.

What are the possible risks of taking part?

The study involves having extra blood tests taken in the Clinical Research Facility in St. James's
Hospital in addition to routine blood tests being taken at your Mater Hospital clinic appointment.
When you give blood, you may feel faint, or experience mild pain, bruising, irritation or redness at the site. In very rare cases, you may get an infection.
The exercise programme in which you may be asked to participate is carefully supervised by physiotherapists from Trinity College Dublin, and is very safe. You will only be invited to join the study if your doctors feel that you would be well enough to participate in the exercise programme if randomised into this arm.

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

Your safety while taking part in a study is most important. If you feel that you have been injured because of taking part please tell your study doctor or physiotherapist. Our

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

research is covered by an insurance policy in ICORG. The doctors, nurses and other clinical staff involved are covered under the Clinical Indemnity Scheme.

Will my taking part in this study be kept confidential?

All of the blood samples, questionnaires and other data will be coded with an identification number and will not be labelled with your name or any other information that directly identifies you. The connection between the code and you will be kept by the research team in St. James's Hospital. Your blood samples and any paper-based data will be kept in secure storage. Electronic (computerised) data will be stored on password-protected machines and servers.

Who will have access to my sample?

The chief investigator, Prof Stephen Finn, his research team and their collaborators will have access to your samples. Anyone who works with your samples will hold your information and results in confidence.

Where will my sample be stored?

If you consent to the study your blood samples, questionnaires and other data will be securely stored in Prof Stephen Finn's laboratory in St James Hospital.

What about the future use of my sample for research?

Samples and data will be stored securely for ten years with the option to seek ethical permission for a longer storage time.
Future research may involve tests that your samples would be suitable for. We will not be able to contact you to ask permission for each individual future study but ask you now for your overall permission to use your donated samples for research purposes. Ethical approval from the St. James's and Tallaght joint research ethics committee will be sought before any future research is carried out.
If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

What are the costs of taking part in this study?

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

You will not be charged for the cost of tests done for the purpose of this study. You will not be reimbursed for your travel costs or parking for your three visits. If you are asked to partake in the exercise aspect of the study you will be reimbursed for your parking fee when attending the classes.

Who has reviewed and approved this study?

This study has been approved by the Mater Hospital Research Ethics Committee.

Contact for further information

If you have any further questions about the study or if you wish to withdraw from the study please contact your doctor or the physiotherapist responsible for your exercise routine. If you wish to withdraw, you may do so without giving a reason and your future treatment will not be affected. Your samples will continue to be stored as part of the study, however you may request to have your samples destroyed and removed from the trial. In this case any remaining samples, which have not yet been analysed, will be destroyed.

For additional information now or any future time please contact:

Chief Investigator:	Prof. Stephen Finn	Telephone:	087 6577927
Physiotherapist:	Grainne Sheill	Telephone:	087 6577927

Thank you for your time.

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Appendix 10: Sample ExPeCT Consent Form

ExPeCT Trial (Exercise, Prostate cancer and Circulating Tumour cells)

Informed Consent Form

Site Doctor/Principal Investigator:	Prof Liam Grogan
Study Doctor Address:	Beaumont Hospital, Beaumont, Dublin 9.
ICORG Study Number:	ICORG 15-21
Name of Institution leading the Research:	Trinity College Dublin
Chief Investigator:	Prof Stephen Finn

Sponsor/Supporter Name and Address: ICORG – the All Ireland Cooperative Oncology Research Group (ICORG), 60 Fitzwilliam Square North, Dublin 2, Ireland.

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

Please write your initials in each box

1. I confirm that I have been given a copy of the Patient Information Leaflet ICORG Version 1.0 10-Aug-2015, BH Version 2.0 07-Sept-2015. I have read the patient information leaflet or it has been read to me. This information was explained to me and my questions were answered. ☐

2. I understand and agree to provide a blood sample for research purposes. ☐

3. I understand that this is a randomised trial and that I may or may not be asked to participate in the exercise routine. I agree to take part in the exercise if I am requested to do so. ☐

4. I understand that my treating doctor will not be informed of the results unless it is relevant to my treatment. ☐

5. I understand that I must attend the Clinical Research Facility in St. James's Hospital to donate blood for the study and if I am randomised to participate in the exercise aspect of the study. ☐

6. I understand that data related to me collected during this study will be processed and analysed as is required by this clinical research study in the department of Histopathology in Trinity College Dublin and St. James's Hospital and according to the Data Protection Act. ☐

7. I understand that my samples may be used for research as described in the Patient Information Leaflet. ☐

8. I understand and agree to allow my data and samples to be used for future research. Before any future research is carried out the ethics committee must agree with the research. If you do not consent to the future use of your samples for research you may still participate in this study.

YES	NO
☐	☐

Website: www.beaumont.ie

Ospidéal Beaumont

BEAUMONT HOSPITAL
P. O. Box 1297 Beaumont Road Dublin 9
Telephone: 809 3000 / 837 7755 Facsimile: 837 6982

9. I give permission to access my archival tissue sample and to use this for research as described in the Patient Information Leaflet and that this may involve the consumption of any residual material. Any residual material will be returned to Beaumont Hospital. ☐

10. I understand that I am free to withdraw from the study at any time and that this will not affect my standard treatment. ☐

11. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient (Print)	Signature of Patient	Date

_____	_____	_____
Name of Witness (Print) *(if required)*	Signature of Witness	Date

Name of Study Doctor (Print)	Signature of Study Doctor
Or Study Co-ordinator (Print)	**Or** Study Co-ordinator
Or Research Nurse (Print)	**Or** Research Nurse
Or Person delegated by CI/PI (Print)	**Or** Person delegated by CI/PI

Appendix 11: ExPeCT Case Report Form

Baseline (T0) Patient Data Sheet **ExPeCT - ID** EXP ☐☐☐ **Date of Birth** (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Date of Assessment (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Demographics

Study Arm
- Exercise intervention group ☐
- Non-exercise comparison group ☐

Primary Hospital

- Dublin (St James's) ☐
- Dublin (Mater) ☐
- Dublin (Tallaght) ☐
- Dublin (Beaumont) ☐
- Dublin (St Luke's) ☐
- Guy's Hospital, UK ☐

Clinical Measurements

- Height ☐☐☐ cm
- Weight ☐☐☐.☐ Kg
- Waist circumference ☐☐☐ cm
- Blood pressure ☐☐☐ / ☐☐☐ mmHg (*systolic* / *diastolic*)

Details of Prostate Cancer

Date of histological diagnosis (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Tumour histology, histologic type (Please tick relevant box)

- Adenocarcinoma ☐
- Small cell neuroendocrine carcinoma ☐
- Other (please specify) ☐

Baseline (T0) Patient Data Sheet

ExPeCT- ID EXP ☐☐☐

Date of Birth (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Initial Gleason grade *3-5* ☐ + *3-5* ☐ = *6-10* ☐

Initial TNM status:

Primary tumour (T)

TX ☐

T0 ☐

T1 ☐

T2 ☐

T3 ☐

T4 ☐

Regional lymph nodes (N):

NX ☐

N0 ☐

N1 ☐

N2 ☐

Distant metastasis (M):

MX ☐

M0 ☐

M1 ☐

Initial treatment (Tick all that apply)

Surgery ☐ Radiotherapy ☐ Hormones ☐

Date of first relapse (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Baseline (T0) Patient Data Sheet **ExPeCT - ID EXP** ☐☐☐ **Date of Birth** (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Scans and Imaging

Performed as part of most recent routine assessment

CT ☐ YES ☐ NO (Tick box, if yes record date of scan, location of metastases and number of lesions)

Date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Location of metastases (Tick all relevant boxes)

Pelvis ☐ Visceral ☐ Spinal ☐ Femur ☐ Other (specify) ☐ _____

Total number of lesions if available (NA if not available) ☐☐

Overall summary

Stable metastatic disease ☐ Increased disease burden (since previous scan) ☐

Other (specify) ☐ _____

MRI ☐ YES ☐ NO (Tick box, if yes record date of scan, location of metastases and number of lesions)

Date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Location of metastases (Tick all relevant boxes)

Pelvis ☐ Visceral ☐ Spinal ☐ Femur ☐ Other (specify) ☐ _____

Total number of lesions if available (NA if not available) ☐☐

Overall summary

Stable metastatic disease ☐ Increased disease burden (since previous scan) ☐

Other (specify) ☐ _____

Baseline (T0)
Patient Data Sheet

ExPeCT - ID
EXP ☐☐☐

Date of Birth (dd/mmm/yyyy)
☐☐ ☐☐☐ ☐☐☐☐

Bone Scans ☐ YES ☐ NO (Tick box, if yes record date of scan, location of metastases and number of lesions)

Date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Location of metastases (Tick all relevant boxes)

Pelvis ☐ Visceral ☐ Spinal ☐ Femur ☐ Other (specify) ☐ _____

Total number of lesions if available (NA if not available) ☐☐

Overall summary

Stable metastatic disease ☐ Increased disease burden (since previous scan) ☐

Other (specify) ☐ _____

Baseline (T0) Patient Data Sheet **ExPeCT- ID** EXP ☐☐☐ **Date of Birth** (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Haematology

Date of sample (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Test (units)	If test is performed in different units, please specify units	Results	If outside lab normal range, please state significance
Total PSA (ng/mL)			NCS ☐ CS ☐
Haemoglobin (g/dL)			NCS ☐ CS ☐
White cell count (10^9/L)			NCS ☐ CS ☐
Platelet count (10^9/L)			NCS ☐ CS ☐

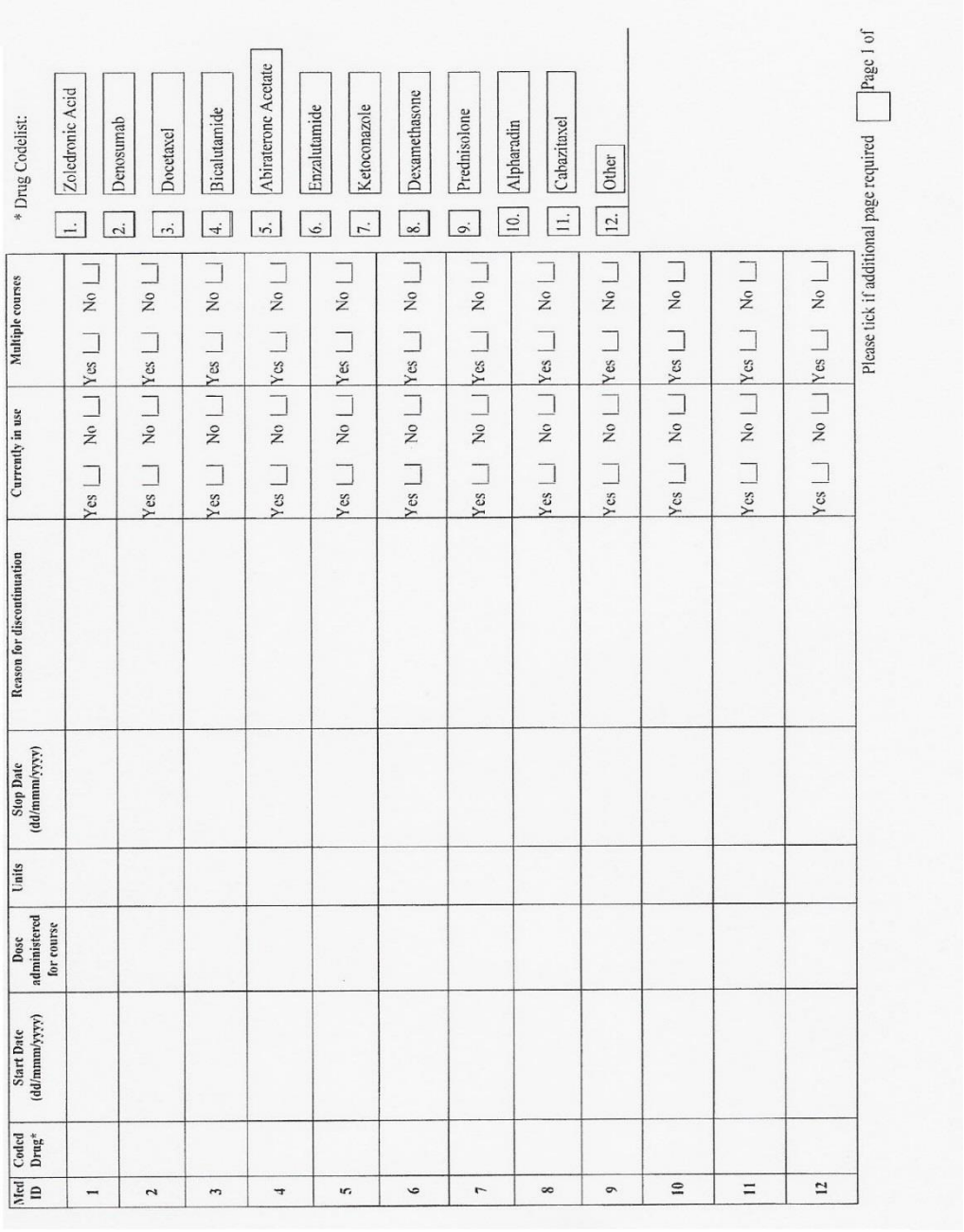
NCS Not Clinically Significant
CS Clinically Significant

Baseline (T0)
Patient Data Sheet

ExPeCT - ID
EXP ☐☐☐

Date of Birth (dd/mmm/yyyy)
☐☐ ☐☐☐ ☐☐☐☐

Details of Previous and Current Systemic Therapy



* Drug Codelist:

1. Zoledronic Acid
2. Denosumab
3. Docetaxel
4. Bicalutamide
5. Abiraterone Acetate
6. Enzalutamide
7. Ketoconazole
8. Dexamethasone
9. Prednisolone
10. Alpharadin
11. Cabazitaxel
12. Other

Page 1 of ☐

Please tick if additional page required

Med ID	Coded Drug*	Start Date (dd/mmm/yyyy)	Dose administered for course	Units	Stop Date (dd/mmm/yyyy)	Reason for discontinuation	Currently in use	Multiple courses
1							Yes ☐ No ☐	Yes ☐ No ☐
2							Yes ☐ No ☐	Yes ☐ No ☐
3							Yes ☐ No ☐	Yes ☐ No ☐
4							Yes ☐ No ☐	Yes ☐ No ☐
5							Yes ☐ No ☐	Yes ☐ No ☐
6							Yes ☐ No ☐	Yes ☐ No ☐
7							Yes ☐ No ☐	Yes ☐ No ☐
8							Yes ☐ No ☐	Yes ☐ No ☐
9							Yes ☐ No ☐	Yes ☐ No ☐
10							Yes ☐ No ☐	Yes ☐ No ☐
11							Yes ☐ No ☐	Yes ☐ No ☐
12							Yes ☐ No ☐	Yes ☐ No ☐

Appendix 12: ExPeCT Subjective Questionnaire

The ExPeCT Trial:

Exercise, Prostate Cancer and Circulating Tumour Cells

Participant number: _____

Date of Birth: _____

Date of Questionnaire:_____

Is this the first, second or third time you have filled in this questionnaire?

1st ☐ 2nd ☐ 3rd ☐

Background details

1. What age were you when you were diagnosed with prostate cancer? _____

2. How would you describe your race / ethnic background?

White/Caucasian ☐ Black/Afro-Caribbean ☐ Asian ☐

3. What is your current marital status?

Married ☐ Divorced/Separated ☐ Widowed ☐

4. What is your current living arrangement?

Alone ☐ With wife ☐ With other family ☐

Assisted Living ☐ Nursing ☐ Other ☐

5. What is your current work status?

Full-time ☐ Part-time ☐ Retired ☐

Disabled ☐ Unemployed ☐

For the following questions please circle the appropriate answer:

6. Have you been diagnosed with any of the following medical conditions?'

(a) High blood pressure	YES	NO
(b) Diabetes mellitus	YES	NO
(c) High cholesterol	YES	NO
(d) Myocardial infarction (heart attack)	YES	NO
(e) Angina pectoris	YES	NO
(f) Atrial fibrillation	YES	NO
(g) Congestive heart failure	YES	NO

7. Have you regularly taken any of these medications *in the last two years*?

(a) Non-steroidal anti-inflammatory drugs (NSAIDs)

(i) Aspirin	YES	NO
(ii) Ibuprofen (e.g. Advil, Motrin, Nuprin, Medipren)	YES	NO
(iii) Other: _____	YES	NO

(b) "Statin" cholesterol-lowering drugs

(i) Lovastatin (e.g. Mevacor, Altocor)	YES	NO
(ii) Simvastatin (e.g. Zocor)	YES	NO
(iii) Pravastatin (e.g. Pravachol, Pravigard)	YES	NO
(iv) Atorvastatin (e.g. Lipitor)	YES	NO

(c) Beta blocker drugs

(i) Metoprolol (e.g. Lopressor, Toprol)	YES	NO
(ii) Atenolol (e.g. Tenormin)	YES	NO
(iii) Nadolol (e.g. Corgard)	YES	NO

(iv) Other: _____ YES NO

(d) Antidepressants: Selective serotonin reuptake inhbitors (SSRIs)

(i) Citalopram (e.g. Celexa) YES NO

(ii) Escitalopram (e.g. Lexapro) YES NO

(iii) Fluoxetine (e.g. Prozac) YES NO

(iv) Paroxetine (e.g. Paxil) YES NO

(v) Sertraline (e.g. Zoloft) YES NO

(vi) Fluvoxamine (e.g. Luvox) YES NO

(e) Other antidepressants

(i) Amitriptyline (e.g. Elavil, Endep) YES NO

(ii) Imipramine (e.g. Tofranil) YES NO

(iii) Nortriptyline (e.g. Pamelor) YES NO

(iv) Other: _____ YES NO

(f) Sleeping tablets

(i) Diazepam (e.g. Valium) YES NO

(ii) Alprazolam (e.g. Xanax) YES NO

(iii) Lorazepam (e.g. Ativan) YES NO

(iv) Chlordiazepoxide (e.g. Librium) YES NO

(g) Diabetes medications

(i) Insulin YES NO

(ii) Metformin YES NO

(iii) Rosiglitazone (e.g. Avandia) YES NO

(iv) Pioglitazone (e.g. Actos) YES NO

Smoking and alcohol

Please circle the most appropriate answer:

1. Do you currently smoke cigarettes? (exclude pipe or cigars)
YES NO

2. If you answered YES to question 2.1, how many cigarettes do you smoke per day?

1-4 *5-14* *15-24* *25-34* *35-44*
45 or more

3. In a typical week over the past three months, on how many days did you consume an alcoholic beverage of any type?

No days *1 day per week* *2 days per week*
3 days per week

4 days per week *5 days per week* *6 days per week*
7 days per week

4. In a typical month, what is the largest number of drinks of beer, wine and / or spirits you have in one day?

None *1-2 drinks per day* *3-5 drinks per day*
6-9 drinks per day *10-14 drinks per day*
15 or more drinks per day

5. In a typical week during the past three months, how often did you drink alone?

Never / I don't drink *Less than once a month*
Once or twice per week *Three to five times per week*
Almost every day

6. If you answered question 2.5 with anything other than "never", on those days when you drank alone, how many drinks did you typically consume?

1 Drink *2 Drinks* *3-4 Drinks*
5-6 Drinks *More than 7 drinks*

Sleep (Pittsburgh Sleep Quality Index)

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

Stress (Perceived Stress Scale – 4)

The questions in this section ask you about your feelings and thoughts *during the last month*.

In each case, please indicate your response by placing an "X" over the circle representing *how often* you felt or thought a certain way.

	Never	Almost never	Sometimes	Fairly often	Very often
1. In the last month, how often have you felt that you were unable to control the important things in your life?	O	O	O	O	O
2. In the last month, how often have you felt confident about your ability to handle your personal problems?	O	O	O	O	O
3. In the last month, how often have you felt that things were going your way?	O	O	O	O	O
4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	O	O	O	O	O

Depression (PHQ-9)

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

Quality of Life (FACT-P)

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.**

	PHYSICAL WELL-BEING	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

	SOCIAL/FAMILY WELL-BEING	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	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	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

	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

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Memory and Cognition

Please circle the most appropriate answer.

Over the past three months:

1	Do you have more trouble than usual remembering recent events?	YES	NO
2	Do you have more trouble than usual remembering a short list of items, such as a shopping list?	YES	NO
3	Do you have trouble remembering things from one second to the next?	YES	NO
4	Do you have difficulty in understanding or following spoken instructions?	YES	NO
5	Do you have more trouble than usual following a group conversation or a plot in a TV programme due to your memory?	YES	NO
6	Do you have trouble finding your way around familiar streets?	YES	NO

Physical activity

Please circle the most appropriate answer:

1. Do you have difficulty climbing a flight of stairs or walking eight blocks (about a mile) due to physical impairment?

YES NO

2. What is your usual walking pace outdoors? *Please tick:*

Unable to walk eight blocks or climb a flight of stairs due to physical impairment.	
Easy, Casual *(Less than 2mph)*	
Normal, average *(2-2.9mph)*	
Brisk pace *(3-3.9mph)*	
Very brisk/striding *(4mph or faster)*	

3. How many flights of stairs (not steps) do you climb daily? (Do not include time spent on exercise machines)

No flights 1-2 flights 3-4 flights

5-9 flights 10-14 flights 15 or more flights

4. In an average week, on how many days do you usually exercise (include brisk walking or more strenuous activity)?

None One Two Three

Four Five Six Seven

5. During the last three months, what was your **average total time per week** at each of these activities?

	NONE	1-4 minutes	5-19 minutes	20-39 minutes	40-80 minutes	1.5 hours	2-3 hours	4 ho
Walking to work or for exercise *(including golf)*								
Jogging *(slower than 10 minutes per mile)*								
Running *(10 minutes per mile or faster)*								
Bicycling *(including stationary machine)*								
Lap swimming								
Tennis								
Squash or racquetball								
Other aerobic exercise *(e.g. exercise classes etc)*								
Other lower intensity exercise *(e.g. yoga, bowling)*								
Moderate outdoor work *(e.g. gardening, yardwork)*								

	NONE	1-4 minutes	5-19 minutes	20-39 minutes	40-80 minutes	1.5 hours	2-3 hours	4-6 hours
Heavy outdoor work *(e.g. digging, chopping)*								
Weight training / resistance exercise for **arms**								
Weight training / resistance exercise for **legs**								
Standing or walking around work								
Standing or walking around home								

Sitting at work or commuting									
Sitting at home while watching TV / DVD									
Other sitting at home									

Diet

1. What type of milk do you use most often?

   None Skimmed Milk Low-fat Milk

   Whole milk/ Full fat milk Super / Fortified Milk Soya Milk

   Other (Please specify _____)

2. How much milk do you drink each day?

   None Half Pint (284ml) One Pint (568ml)

   One Litre More than one later

3. Please indicate how often, on average, over the past three months, you have eaten or drank the specified amount of each of the following foods and drinks.

		None	< 1 a month	1-3 a month	1 a week	2-4 a week	5-6 a week	1 a day	2-3 a day	4-5 a day	6+ a day
1.	Cup of tea with caffeine *(8 oz.) – includes green tea*										
2.	Yoghurt *(1 cup)*										
3.	Cottage or ricotta cheese *(1/2 cup)*										
4.	Cream cheese *(1 ounce)*										
5.	Other regular cheese, alone or as part of a dish *(1 slice or 1 ounce)*										
6.	Other low-fat cheese, alone or as part of a dish *(1 slice or 1 ounce)*										
7.	Ice cream *(1/2 cup)*										
8.	Processed meats, sausage, salami, bologna, hotdog *(1 slice or piece)*										
9.	Beef, pork, lamb: as a sandwich or mixed dish, *e.g. stew, casserole, lasagna*										
10.	Beef, pork, lamb: as a main dish, *e.g. steak, roast*										

5. **(a)** Have you regularly taken vitamin D since your prostate cancer diagnosis?

YES NO

(b) If you answered "yes" to question 9.4(a), please indicate your daily dose, the year you started taking vitamin D, the duration for which you have taken vitamin D since your diagnosis, and whether you are currently taking vitamin D.

(i) Daily dose: _____IU

(ii) Year you started taking vitamin D: __ __ __ __

(iii) Duration of taking vitamin D:

(Only include time spent taking vitamin D <u>after</u> you were diagnosed with prostate cancer):

Less than 6 months 6-12 months 1-2 Years 3+ Years

(iv) Are you currently taking vitamin D?

Yes No

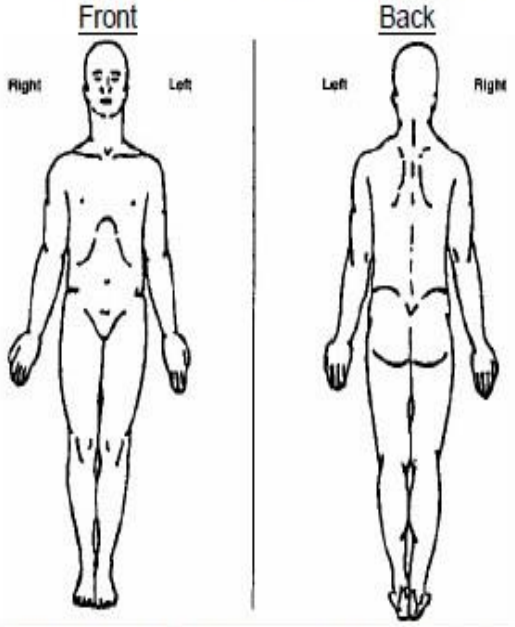
Pain

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

No Pain — Pain As Bad As You Can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain 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 housework)

☐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. Sleep

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

G. Enjoyment of life

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10
Does Not Interfere — Completely Interferes

Appendix 13: ExPeCT Exercise Class Document

Exercise Class:

Verbal consent to participate in class: ☐

Subjective Report:

_____

_____

_____

Blood Pressure and Heart Rate

Pre Exercise (in standing): _____/____mmHg _____bpm

Post Exercise: _____/____mmHg _____bpm

Pre-exercise stretching: March on the spot, arm swings, shoulder rolls, elbow-flexes, wrist turns, knee flexes and ankle pumps ☐

	Time	Intensity	bpm	Mode	Completed (√)
Warm up		(<40% HRR)			
Aerobic Component					
Cool Down		(<40% HRR)			

Post exercise stretching: Quads, Hamstrings, Calf (Held for 10-30 seconds x 2-4 reps, R+L) ☐

No adverse effects to exercise class: ☐

Was requested participant to complete ___ additional exercise session, as per above intensity and duration, as part of home exercise plan this week.

Additional Comments:

_____

_____

Signed: **Date:**

Appendix 14: ExPeCT Off Study Form

Off Study Form **ExPeCT - ID** **Date of Birth** (dd/mmm/yyyy)

EXP ☐☐☐ ☐☐ ☐☐☐ ☐☐☐☐

Primary Hospital

Dublin (St James's)	☐	Dublin (Beaumont)	☐
Dublin (Mater)	☐	Dublin (St Luke's)	☐
Dublin (Tallaght)	☐	Guy's Hospital, UK	☐

This off study form must be completed for all patients, whether they have completed the study or have withdrawn from the study or had to stop their participation for any reason.

Date Off Study (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

PLEASE SPECIFY THE REASON WHY THE PATIENT IS NOW OFF THE STUDY (please tick one)

☐ Study completion

☐ Extraordinary medical circumstances Please specify _____

☐ Sponsor decision

☐ Lost to follow up Date of last contact (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

☐ Withdrawal of patient consent Date of withdrawal (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Reason for withdrawal _____

☐ Death Date of death (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Cause of death _____

☐ Other

Please specify _____

Previous assessment forms completed: ☐ YES ☐ NO ☐ N/A

Investigator's name _____

Investigator's signature: _____

Date (dd/mmm/yyyy): ☐☐ ☐☐☐ ☐☐☐☐

Appendix 15: ExPeCT Incident Report Form

Incident Report Form **ExPeCT - ID** EXP ☐☐☐ **Date of Birth** (dd/mmm/yyyy) ☐☐ ☐☐☐ ☐☐☐☐

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of Incident	Expected	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced dose 5 = Increased dose 6 = Delayed dose	1 = Resolved, no sequel 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-not treated 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (If yes, complete SI form)

Incident	Start Date	Stop Date	Severity	Relationship to Study Treatment	Action Taken	Outcome of Incident	Expected?	Serious Incident?	Initials
1.									
2.									
3.									