BMJ Open

Can exercise suppress tumour formation and growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining safety, feasibility and efficacy.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014458
Article Type:	Protocol
Date Submitted by the Author:	26-Sep-2016
Complete List of Authors:	Hart, Nicolas; Edith Cowan University, Exercise Medicine Research Institute Newton, Robert; Edith Cowan University, Exercise Medicine Research Institute Spry, Nigel; Sir Charles Gairdner Hospital, Department of Radiation Oncology; Edith Cowan University, Exercise Medicine Research Institute Taaffe, Dennis; Edith Cowan University, Exercise Medicine Research Institute Chambers, Suzanne; Griffiths University, Menzies Health Institute; Edith Cowan University, Exercise Medicine Research Institute Feeney, Kynan; Edith Cowan University, Exercise Medicine Research Institute; St John of God Hospital, Department of Medical Oncology Joseph, David; Sir Charles Gairdner Hospital, Department of Radiation Oncology; Edith Cowan University, Exercise Medicine Research Institute Redfern, Andrew; Fiona Stanley Hospital, Department of Medical Oncology; University of Western Australia, School of Medicine and Pharmacology Ferguson, Tom; Fiona Stanley Hospital, Department of Medical Oncology Galvão, Daniel; Edith Cowan University, Exercise Medicine Research Institute
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine
Keywords:	tumour biology, tumour activity, resistance training, isometric training, aerobic exercise

Can exercise suppress tumour formation and growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining safety, feasibility and efficacy.

Nicolas H. Hart, PhD [1]; Robert U. Newton, PhD [1]; Nigel A. Spry, MD PhD [1,2,3]; Dennis R. Taaffe, PhD DSc MPH [1]; Suzanne K. Chambers, PhD [1,4]; Kynan T. Feeney, MD MPH [1,5,6]; David J. Joseph, MD [1,2]; Andrew D. Redfern, MD, PhD [7,8]; Tom Ferguson, MD [7]; Daniel A. Galvão, PhD [1]

[1] Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia
[2] Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia
[3] Department of Radiation Oncology, Genesis CancerCare, Perth, WA, Australia
[4] Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia
[5] Department of Medical Oncology, St John of God Hospital, Perth, WA, Australia
[6] School of Medicine, University of Notre Dame Australia, Perth, WA, Australia
[7] Department of Medical Oncology, Fiona Stanley Hospital, Perth, WA, Australia
[8] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

Running Title: *Exercise and tumour suppression.*

Corresponding Author:
Dr. Nicolas H. Hart – PhD, AES, CSCS, ESSAM.
Exercise Medicine Research Institute
Edith Cowan University, 270 Joondalup Drive, Joondalup
Perth, Western Australia, Australia – 6027.
Ph: +61 8 6304 3436
Fax: +61 8 6304 2499
Email: n.hart@ecu.edu.au

Key Words: tumour biology; tumour activity; isometric; resistance; aerobic; flexibility.

ABSTRACT

Introduction: Exercise positively alters tumour biology through numerous modulatory and regulatory mechanisms in response to a variety of modes and dosages, evidenced in pre-clinical models to date. Specifically, localised and systemic biochemical alterations produced during and following exercise may suppress tumour formation, growth and distribution by virtue of altered epigenetics and endocrine-paracrine activity. Given the impressive ability of targeted mechanical loading to interfere with metastasis-driven tumour formation in human osteolytic tumour cells, it is of equal interest to determine whether a similar effect is observed in sclerotic tumour cells. The study aims to examine 1) whether a targeted and supervised exercise program can suppress sclerotic tumour growth and activity in advanced prostate cancer patients with bone metastases in humans; and 2) the feasibility and safety of combining spinal isometric training (SIT) with a modular multi-modal exercise program (M3EP).

Methods and Analysis: A single-blinded, two-armed, randomised, controlled and explorative phase 1 clinical trial combining spinal isometric training with a modular multi-modal exercise program in 40 men with advanced prostate cancer and stable sclerotic spinal metastases. Participants will be randomly assigned to (1) the exercise intervention or (2) usual medical care. The intervention group will receive a 3-month, supervised and individually tailored modular multi-modal exercise program with spinal isometric training. Primary and secondary endpoints will be measured at baseline and following the intervention.

Ethics and Dissemination: Ethics approval was obtained from the Human Research Ethics Committee (HREC) of Edith Cowan University. If proven to be safe, feasible and effective, this study will form the basis of future phase II and III trials in human patients. To reach a maximum number of clinicians, practitioners, patients and scientists, outcomes will be disseminated through national and international clinical, conference and patient presentations, as well as publication in high-impact, peer-reviewed academic journals.

Trial Registration: ACTRN-12616000179437

STRENGTHS AND LIMITATIONS

- This is a novel, phase I randomised controlled trial in humans exploring the effect of targeted exercise on tumour morphology and circulating metastatic tumour biomarkers using a sclerotic skeletal metastases model in prostate cancer patients.
- The study is principally aimed at establishing feasibility and safety, and may lack statistical power or a suitable length of intervention to determine the efficacy of exercise on tumour biology and metastatic tumour biomarkers.

INTRODUCTION

Bone is the most common location for metastatic prostate carcinoma, with skeletal lesions identified in over 80% of advanced prostate cancer patients[1-5]. These lesions predominantly present as sclerotic (osteoblastic) and primarily reside in the axial skeleton (spine, pelvis or ribs)[6-8], presenting a considerable challenge for practitioners to deliver exercise interventions to this population[9,10]. In particular, advanced cancer patients have historically been excluded from exercise intervention studies and community-based supervised exercise programs due to potential adverse skeletal events. Clinically, bone metastases present as a major concern with patients experiencing severe bone pain, increased risk of skeletal complications, spinal compression, hypercalcaemia and decreased physical function and quality of life[9-13]. Consequently patients with metastatic bone disease experience significant morbidity with many barriers to exercise participation, thus strategies to safely and effectively reduce the burden of bone metastatic disease have a high degree of clinical importance.

Despite the unequivocal benefits of physical activity and exercise for cancer patients[14-25], fear of adverse skeletal events has led to reduced uptake of physical activity by patients, and reduced referrals to exercise programs by clinicians[9,10,18]; a cycle which exacerbates musculoskeletal fragility and tumour progression. In recent times, Galvão and colleagues[9,10,21]

designed a modular, multi-modal exercise program (M3EP) to provide this population with safe and effective exercise modified to avoid direct loading of lesion sites; the first of its kind in exercise oncology. Preliminary findings have been promising, with exercise shown to be well tolerated (safe and efficacious); delivering clear improvements in physical function, physical activity levels and lean mass in these patients[10,21]. However, it is not yet known whether direct loading of lesion sites in bone metastases is safe to deliver, or therapeutically advantageous in providing adjuvant, synergistic or independent health benefits or tumoral modulations in advanced prostate cancer patients.

Exercise positively alters tumour biology via numerous mechanisms in response to a variety of modes and dosages[26-33]. Specifically, exercise regulates endocrine-paracrine activity, immune system function, blood glucose levels, blood cholesterol levels, insulin response and body composition[34-41]; whilst epigenetically modulating tumour cell proliferation, telomere length, telomere enzyme activity, tumour vascularity, oxidative stress capacity, platelet cloaking and platelet adhesion[26-33,42-47]. Although these regulatory and modulatory outcomes interact, the ability to suppress tumour formation, growth and spread by virtue of altered epigenetics and endocrine-paracrine activity through exercise is of particular interest. This emerging field of mechanomics in exercise oncology (biological alterations driven from biomechanical stimuli)[48-51] presents practitioners with a unique opportunity to potentially suppress metastatic prostate carcinoma in bone through targeted exercise interventions.

Direct loading of animal metastatic bones containing human breast cancer tumour cells supports this new direction, successfully interfering with metastasis-driven tumour formation[50] by delivering suppressive localised modulatory changes to the tumour microenvironment, while preserving bone material, structure and strength[49,50]. Given the impressive ability of mechanical loading to epigenetically interfere with metastasis-driven tumour formation in

osteolytic tumour cells, it is of equal interest to determine whether mechanical loading is also able to alter metastasis-driven tumour formation in sclerotic tumour cells. This may also prove to be an effective adjuvant intervention to alleviate bone pain, preserve musculoskeletal strength, and suppress sclerotic tumour expansion. To our knowledge, no studies have directly targeted sclerotic lesion bone sites in prostate cancer patients with skeletal metastases through controlled, localised exercise programs.

The aim of this study is to examine whether a targeted and supervised exercise program can effectively suppress sclerotic tumour formation, growth and activity in advanced prostate cancer patients with bone metastases in humans; and to examine the feasibility, safety and efficacy of advancing the M3EP program by including spinal isometric training (SIT) to produce targeted and localised exercise of muscle surrounding sclerotic lesions. We hypothesise that the M3EP-SIT program will reduce the rate of sclerotic tumour progression; alleviate bone pain; not increase the incidence of skeletal fractures; act to preserve muscle and bone material, structure and strength; improve physical fitness and functional ability; and increase quality of life and psychosocial wellbeing. We envisage the outcomes of this phase I clinical trial will advance preliminary clinical knowledge pertaining to exercise prescription for cancer patients with metastatic prostate carcinoma, directly loading bone with lesions to modulate tumour biology, thereby informing phase II and phase III clinical trials in an effort to establish new clinical exercise guidelines in this high risk and unique population.

METHODS AND ANALYSIS

Study Design

This is a single-blinded (investigators blinded to group allocation), two-armed, randomised and controlled (exercise versus usual care) explorative phase 1 clinical trial which will examine the safety, feasibility and efficacy of combining spinal isometric training with a

modulatory, multi-modal exercise program (M3EP-SIT) in men with advanced prostate cancer and sclerotic spinal bone metastases. The exercise group (intervention arm) will receive an individually tailored and supervised 3-month (12 weeks) exercise program involving resistance, aerobic and flexibility exercises in addition to usual medical care. The control group will receive usual medical care during this time and will be asked not to change their baseline levels of physical activity. Following the trial, the control group will be offered the same exercise program if the intervention is deemed to be safe, feasible and efficacious.

Recruitment

Patients will be recruited by invitation of their cancer specialist (radiation, medical or surgical oncologist), who will refer clinically eligible patients with a study information sheet to a study coordinator. If patients are interested in participation, and their eligibility is confirmed, they will receive an informed consent document to read and sign before undertaking baseline measurements prior to randomisation (Figure 1).

Randomisation

Patients will be randomly allocated in a ratio of 1:1 to the two study arms: exercise (M3EP-SIT) or usual care, stratified by age (≤70 years, >70 years) and time since completion of chemotherapy or radiotherapy or change in hormone therapy (<3 months, ≥3 months). All patients will be on androgen deprivation therapy (ADT) prior to, and during this study. A research officer with no patient contact will be responsible for randomisation of patient's into either group by using a computer random assignment programme. Study investigators and exercise physiologists conducting testing procedures will be blinded to group allocation. Only exercise physiologists not in the research team will be permitted to deliver the exercise intervention to participants in order to maintain integrity of the blinding process.

Participants

Forty men (20 subjects per arm) with prostate cancer and established, stable bone metastases in thoracic and/or lumbar vertebrae, who have not engaged in regular exercise (undertaking structured aerobic or resistance training two or more times per week) within the past 3 months will serve as participants. Due to the novelty of this explorative phase 1 clinical trial, our sample size was chosen based on previous pre-clinical animal studies[26,30,32,50], human pilot studies[31,33] and consideration of recruitment ability for advanced prostate cancer patients with bone metastases during the trial. Specifically, to achieve 80% power at an alpha level of 0.05 (two-tailed), 16 subjects per group would be required to demonstrate a meaningful difference (effect size ≥1.0) at the completion of the study for the primary endpoint, and most secondary endpoints. To account for up to a 25% attrition rate, 40 subjects will be randomised evenly to each study arm (Exercise: n=20; Control: n=20).

Patients will be excluded from this trial if they have commenced chemotherapy; if they are receiving radiotherapy for any spinal bone metastases; if they have commenced or changed hormone therapy within 3 months of enrolment; or are currently receiving any other experimental treatments or non-approved therapies. Patients are permitted to receive radiotherapy for non-spinal bone metastases only while enrolled in this trial. Patients require medical clearance prior to enrolment, therefore must achieve an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 1; and must not have any acute illness, significant bone pain, or cardiovascular or neurological disorders that could inhibit exercise participation. All participants must provide written informed consent prior to participation. The protocol has been approved by the Human Research Ethics Committee (HREC) of Edith Cowan University (ECU), Project ID's: 13399 HART and 14146 HART. This trial is also registered with the Australia and New Zealand Clinical Trails Register (ANZCTR), Trial ID: ACTRN-12616000179437.

Measurements

Primary and secondary endpoints will be taken at baseline (Week 0), post-intervention (Week 13) and through-out the 12-week on-trial period (Table 1).

Primary Endpoint

Tumour Morphology and Activity

Tumour morphology will be measured using axial T1-weighted magnetic resonance imaging (MRI) scans (1.5T, Magnetom Essenza, Siemens, Victoria, Australia) in locations where sclerotic lesions have been identified in patients with bone metastases at either thoracic or lumbar spinal regions[52-54]. Location of metastatic lesions will be previously identified through bone scans provided by the radiation oncologist prior to referral to this study. All scans will be performed on the same MRI machine by the same radiologist who will also report on all images obtained. Metastatic tumour biomarkers, HIF-1α and TGF-β will be serologically examined to measure hypoxic activity and transformation-growth activity respectively; identified as synergistic drivers of metastatic tumour progression[55].

Secondary Endpoints

Other Biomarkers

Serological and urianalytical samples will be collected to measure bone metabolic activity and systemic inflammation. Specifically, bone formation marker, amino-terminal propeptide of type 1 procollagen (P1NP); bone resorption marker, amino-terminal collagen type-I telopeptide (NTx); bone disorder marker, alkaline phosphate (ALP), inflammation marker, C-reactive protein (CRP), and fasting glucose and lipid profiles will be examined. Prostate specific antigen (PSA) will also be assessed. All biomarkers will be collected and assessed by the same accredited laboratory (PathWest Diagnostics, Perth, Western Australia).

Anthropometry

Stature will be recorded to the nearest 0.1 cm using a wall-mounted stadiometer (Model 222, Seca, Hamburg, DE), with body mass recorded to the nearest 0.1 kg using an electronic scale (AE Adams CPW Plus-200, Adam Equipment Inc., CT, USA). Waist and hip circumferences are defined as the mid-point between the 10th rib and iliac crest; and the level of the greater trochanter, respectively, with the waist-to-hip ratio calculated. Waist circumference and hip circumference will be measured to the nearest 0.1 cm using a constant-tension, retractable measuring tape (Model 4414, Tech-Med Services, NY, USA). Stature, waist circumference and hip circumference will be performed in triplicate for each participant, with the average of each variable retained for analysis.

Musculoskeletal Health

Whole-body, segmental (axial, appendicular) and regional (spinal, hip, proximal femur) scans will be performed to examine bone area (BA), areal bone mineral content (aBMC), areal bone mineral density (aBMD) and lean mass using Dual-energy X-ray Absorptiometry (DXA; Hologic Discovery A, Waltham, MA). Whole-body and appendicular segmentations will be analysed in accordance with Hart and colleagues[56]. Regional analyses (lumbar spine, total hip, femoral neck, trochanter, Wards triangle) will be performed in accordance with Hologic's manufacturer specifications[57].

Appendicular, non-lesion control sites will be scanned to quantify bone material, structure and strength using peripheral Quantitative Computed Tomography (pQCT; XCT-3000, Stratec, Pzochienheim, Germany). Specifically trabecular, cortical, marrow and total volumetric density (Tb.vBMD, Ct.vBMD, Ma.vBMD, Tt.vBMD); trabecular, cortical, marrow and total cross-sectional area (Tb.Ar, Ct.Ar, Ma.Ar, Tt.Ar); cortical thickness (Ct.Th); stress-strain index (SSIPOL); absolute fracture load (FL.Ab) and relative fracture load (FL.Rel) of the left Femur (4% and 38% slices) and left Tibia (4%, 14%, 38% and 66% slices) will be

measured and analysed in accordance with Hart and colleagues[58]. Muscle cross-sectional area (Mu.Ar) will also be quantified.

Adiposity

Whole-body, segmental and central subcutaneous adipose tissue (fat mass); central visceral adipose tissue (VAT; area, mass and volume); and android to gynoid ratio will be measured using DXA. Whole-body and appendicular segmentations will be generated in accordance with Hart and Colleagues[56]. Fat area (Fa.Ar) and muscle density (Mu.Den) of the thigh and shank segments will be measured using pQCT[58], as an indication of subcutaneous and intramuscular fat infiltration, respectively.

Bone Pain, Program Safety, Tolerance and Adherence

The nature, severity and impact of bone pain will be examined using the FACIT Bone Pain questionnaire at baseline and post-intervention. Program safety will be assessed by recording the incidence and severity of any adverse events and/or skeletal complications through-out the exercise intervention. Adverse events and skeletal complications will also be recorded for the usual care group. Skeletal complications include heightened pain at bone metastatic sites and/or pathological skeletal fractures. Program tolerance will be quantified by measuring bone pain and fatigue at each exercise session through visual analog scales (VAS, 0-10), and by recording the rating of perceived exertion (RPE; Borg Scale, 0-10) after each exercise session. An exercise diary will be maintained for all supervised and self-managed sessions to measure program adherence.

Objective Measures of Physical Function

Muscle strength, aerobic capacity and physical function will be measured through a series of assessments. Muscle strength will be measured using the one repetition maximum (1RM) test for the leg extension exercise. This exercise was chosen as it can be safely

performed by all patients included in this study. The 400m walk test and Timed Up and Go test will be used as measures for aerobic capacity and physical function, respectively. In addition, patients will also undergo a comprehensive balance test (NeuroCom Smart Balance Master, Natus Medical Inc., USA).

Quality of Life, Anxiety, Distress, Insomnia and Physical Activity

Health-related quality of life outcomes for general health, pain, vitality, social functioning, emotional role and mental health will be measured by the Short Form 36 (SF-36, IQOLA) survey. In addition, the EORTC-QLQ-30 (cancer) and EORTC-PR-25 (prostate cancer) survey will also be provided to measure cancer specific indices of quality of life. The Brief Symptom Inventory (BSI-18) will be used to assess psychological distress for anxiety, depression, somatisation and global distress severity domains. The Insomnia Severity Index (ISI) will be used to measure sleep quality disturbance, and the Godin Leisure-Time Exercise questionnaire will examine self-reported physical activity levels.

Exercise Program

Participants assigned to the exercise arm will be required to participate in a modular, multi-modal exercise intervention with spinal isometric training (M3EP-SIT) for 12 weeks (3 months). The combined M3EP-SIT program requires participants to attend three clinic-based exercise sessions each week spanning 60 minutes in duration (including warm-up and cool-down), supervised by an accredited exercise physiologist (AEP; Exercise and Sport Science Australia). Participants will also be asked to perform the SIT program during two additional home-based exercise sessions each week spanning 15 minutes in duration. During combined M3EP-SIT sessions, spinal isometric training will be provided first, followed by the modular multi-modal exercise program (Table 2).

The modular, multi-modal exercise (M3EP) component of the program will be comprised of resistance, aerobic and flexibility exercises in accordance with Galvão and colleagues[9]. This M3EP component is designed to minimise loads on affected skeletal sites through-out the body. Exercise prescriptions will be modified based on the location and extent of bone metastases for all activities (Table 3). Resistance exercise will be set using repetition maximums (RM). Participants will be asked to perform 6 different resistance exercises using major muscle groups, subject to the location and extent of bone metastases, at 10-12 RM for 3 sets per exercise to achieve moderate intensity and volume. Aerobic exercise will be set using age-predicted heart rate maximum (HRmax). Participants will engage in cardiovascular exercise using various modes including treadmill, cycling and rowing ergometers, performed at 60-85% HRmax for 20-30 minutes using heart rate monitors (Polar Electro Oy, Finland). Flexibility exercise will involve static stretching of all joints considered important for function, and for all muscles engaged during the session. All stretches will involve 2-4 sets per muscle group with a 30-60 second hold per set.

The spinal isometric training (SIT) component of the program will comprise of exercises that isometrically load deep spinal muscles. These will be performed 5 times per week. Three sessions will be supervised by an AEP synonymous with the M3EP component at an exercise clinic; with an additional two sessions self-managed by the participant. This SIT component is designed to directly target and stimulate spinal lesion site(s) through muscular contraction, thus isometric exercises have been designed to activate the full spinal column due to the commonality of lesions in thoracic and lumbar regions; the feasibility of which has been demonstrated[59]. The SIT program will require the participants to perform five exercises in whole and partial weight-supported prone and supine positions on the floor, whilst maintaining a neutral spine (isometrically) during gentle and dynamic accessory movements. If floor exercises are contraindicated for the patient due to physical restrictions, alternate seated and

standing isometric exercises are also provided. All patients will be initially provided with familiarisation of breathing technique, trunk stabilisation and hip control. Basic spinal isometric exercises will first be used to ensure safe and correct technique prior to progressing to intermediate or more challenging exercises which include less stability or dynamic accessory movements[60]. Isometric progression of patients from beginner to advanced exercises will be individually determined on the basis of their physical capabilities and known contraindications. An assortment of spinal isometric exercises canvassing the beginner to advanced, floor to standing spectrum are described in Supplementary Tables.

Statistical Analysis

Data will be analysed using SPSS (IBM Corporation; Chicago, IL, USA). Normality of distribution for continuous variables will be determined using the Kolmogorov-Smirnov test and visual inspection of the data. Analyses will include standard descriptive characteristics, t-tests, and two-way (group x time) repeated measures ANOVA (or analysis of covariance as appropriate) to examine differences between groups over time. Any data that is not normally distributed will be log-transformed or non-parametric tests will be used. For categorical variables, the Pearson Chi-square test will be used. An alpha level of $p \leq 0.05$ will be applied to establish statistical significance. Effect sizes will also calculated in accordance with Hopkins[62]: $d \geq 0.2$ is small; $d \geq 0.6$ is moderate; $d \geq 1.2$ is large; $d \geq 2.0$ is very large.

Dissemination

Outcomes of this trial will be broadly disseminated through various communication channels to maximise the potential for further research and development. If proven to be safe, feasible and efficacious, the outcomes will form the basis of phase II and phase III clinical trials. To ensure a high level of delivery to clinicians, practitioners, patients and scientists, outcomes will be disseminated through national and international clinical, patient and conference presentations, as well as publication in high-impact, peer-reviewed journals.

DISCUSSION

Metastatic prostate carcinoma spreads to bone in over 80% of advanced prostate cancer cases and is presently an incurable, yet treatable stage of the disease during palliation[1-8]. Consequently, these patients are provided with a suite of treatments that serve to manage pain and slow tumour progression, including ADT, radiotherapy and chemotherapy. While beneficial, these treatments produce an array of burdensome side-effects leading to considerable morbidity. The effectiveness of exercise as an adjuvant therapy to minimise, manage and in some cases reverse the adversities of primary therapies has been demonstrated[14-25]. Exercise has also shown synergistic potential with primary treatments, subsequently improving their potency; for example, enhancing chemotherapy through increased tumour vascularity to enable greater cytotoxic delivery at tumour sites[26-31]. However, the direct influence of exercise on tumour biology remains largely unknown, despite many hypothesised mechanical and non-mechanical mechanisms of action[26,63-68]. To date, orthotopic animal models have provided compelling new insight into the ability of mechanical stimulation to interfere with tumour-driven remodelling in skeletal tissue containing human breast cancer cells[48-51]. Given that exercise is a dose-dependent mechanical stimulant which can be safely prescribed to advanced prostate cancer patients with bone metastases[9,10], it is of interest to examine whether similar modulatory interference of tumour formation and growth is achievable in humans.

This study will evaluate the safety, feasibility and efficacy of combining spinal isometric training with a modular, multimodal exercise program to provide a non-invasive, low-cost, innovative and scalable therapy in the management of advanced prostate cancer. Specifically, this study will examine the modulatory potential of direct and targeted mechanical loading of sclerotic bone lesions through isometric exercise to deliver muscle contractile forces that may suppress localised tumour formation in spinal bone metastases; mediate systemic

activity of metastatic biomarkers HIF-1α (local hypoxia) and TGF-β (tumour activity); reduce bone pain; and preserve localised and surrounding musculoskeletal mass and structure. In addition, this study will also examine the multidimensional effects of exercise in advanced prostate cancer patients with bone metastases on muscle-bone health; adiposity; physical fitness; functional capacity; and psychosocial health. The outcomes of this study will provide innovative, new evidence that may be used to pursue larger phase II and phase III clinical trials to determine the efficacy of exercise on tumour suppression or regression in patients with sclerotic bone metastases secondary to prostate cancer. The outcomes of this study may also stimulate research into osteolytic or mixed bone metastases models with other primary cancer diagnoses; and may also inform the development of effective pharmaceuticals for treatment. Lastly, this study presents an exercise intervention that, if effective following larger randomised controlled trials, can inevitably be delivered in clinical and community settings by exercise physiologists.

Acknowledgements

The authors would like to thank Miss. Thea Richardson (Australian Prostate Cancer Research), Mr. Kyle Smith (Vario Health Clinic), Mrs. Claire Mason (Exercise Medicine Research Institute) and Mr Derek Atkinson (Consumer Representative) for their guidance and assistance.

Contributors

NHH, DAG, RUN and NAS developed the study concept and protocols and initiated the project. DRT, SKC, DJJ, KTF, ADR and TF assisted in further development of the protocol. NHH, DAG, RUN, DRT and SKC drafted the manuscript. NAS, DJJ, KTF, ADR and TF will provide access to patients. NHH, DAG and RUN will implement the protocol and oversee collection of data. All authors contributed and approved the final manuscript.

Funding

This project is funded by Cancer Council Western Australia (Early Career Investigator Award), and supported by Exercise Sport Science Australia (Clinical Exercise Physiology Research Grant). DAG is funded by Prostate Cancer Foundation of Australia (Movember New Directions Development Award) and Cancer Council Western Australia (Research Fellowship). SKC is supported by Australian Research Council (Professorial Future Fellowship).

Competing Interests

None declared.

Ethics Approval

Human Research Ethics Committee: ECU, Perth, Western Australia, Australia.

REFERENCES

1. Hall CL, Bafico A, Dai J, *et al*. Prostate cancer cells promote osteoblastic bone metastases through Wnts. *Cancer Res*. 2005;65:7554-7560.

2. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. *J Cell Biochem*. 2004;91:718-729.

3. Mundy GR. Metastasis to bone: Causes, consequences and therapeutic opportunities. *Nat Rev Cancer*. 2002;2:584-593.

4. Keller ET, Zhang J, Cooper CR, *et al*. Prostate carcinoma skeletal metastases: cross-talk between tumour and bone. *Cancer and Metastasis Rev*. 2001;20:333-349.

5. Suva LJ, Washam C, Nicholas RW, *et al*. Bone metastasis: Mechanisms and therapeutic opportunities. *Nat Rev Endocrin.* 2011;7:208-218.

6. Guise TA, Mohammad KS, Clines G, *et al*. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. *Clin Cancer Res*. 2006;12:6213-6216.

7. Lee RJ, Saylor PJ, Smith MR. Treatment and prevention of bone complications from prostate cancer. *Bone*. 2011;48:88-95.

8. Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer*. 2005;5:21-28.

9. 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;11:517-523.

10. Cormie P, Newton RU, Spry N, *et al*. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*. 2013;16:328-335.

11. Coleman RE. Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity. *Clin Cancer Res*. 2006;12:6243-6249.

12. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*. 2000;88:2989-2994.

13. Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: Quality-of-life considerations throughout the continuum of care. *Eur Urol.* 2004;46:731-739.

14. Kenfield SA, Stampfer MJ, Giovannucci E, *et al*. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*. 2011;29:726-732.

15. Galvão DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol*. 2005;23:899-909.

16. Newton RU, Galvão DA. Exercise in prevention and management of cancer. *Curr Treat Options Oncol*. 2008;9:135-146.

17. Singh F, Newton RU, Galvão DA, *et al*. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol*. 2013;22:91-104.

18. 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;14:485-493.

19. Buffart LM, Galvão DA, Chinapaw MJ, *et al*. Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer. *Cancer*. 2014;120:294-301.

20. Newton RU, Galvão DA. Exercise medicine for prostate cancer. *Eur Rev Aging Phys Act*. 2013;10:41-45.

21. Cormie P, Galvão DA, Spry N, *et al*. 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*. 2014;22:1537-1548.

22. Hayes SC, Spence RR, Galvão DA, *et al*. Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. *J Sci Med Sport*. 2009;12:428-434.

23. Buffart LM, Galvão DA, Brug J, *et al*. Evidence-based physical activity guidelines for cancer survivors: Current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40:327-340.

24. Galvão DA, Taaffe DR, Spry N, *et al*. 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.

25. Galvão DA, Spry N, Taaffe DR, *et al*. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis*. 2007;10:340-346.

26. Betof AS, Lascola CD, Weitzel DH, *et al*. Modulation of murine breast tumour vascularity, hypoxia and chemotherapeutic response by exercise. *J Natl Cancer Inst*. 2015;107:1-6.

27. Hoffman P. Exercise training, tumour metabolism, tumour-host interaction and lactate shuttle theory. *Front Pharmacol*. 2014.

28. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: A translational perspective. *Brain Behav Immun*. 2013;30:S75–S87.

29. Jones LW, Dewhirst MW. Therapeutic properties of aerobic training after a cancer diagnosis: More than a One-Trick Pony? *J Natl Cancer Inst*. 2014;106:1-3.

30. 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*. 2012;113:263-272.

31. Jones LW, Fels DR, West M, *et al*. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prev Res*. 2013;6:925-937.

32. Wolff G, Balke JE, Andras IE, *et al*. Exercise modulates redox-sensitive small GTPase activity in the brain microvasculature in a model of brain metastasis formation. *PLoS One*. 2014;9:1-8.

33. Glass OK, Inman BA, Broadwater G, *et al*. Effect of aerobic training on the host systemic milieu in patients with solid tumours: An exploratory correlative study. *Br J Cancer*. 2015;112:825-831.

34. Galvão DA, Nosaka K, Taaffe DR, *et al*. Endocrine and immune responses to resistance training in prostate cancer patients. *Prostate Cancer Prostatic Dis*. 2008;11:160-165.

35. Galvão DA, Spry N, Denham J, *et al*. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol*. 2014;65:856-864.

36. Galvão DA, Spry N, Taaffe DR, *et al*. A randomized controlled trial of an exercise intervention targeting cardiovascular and metabolic risk factors for prostate cancer patients from the RADAR trial. *BMC Cancer*. 2009;9:419-426.

37. Galvão DA, Newton RU, Taaffe DR, *et al*. Can exercise ameliorate the increased risk of cardiovascular disease and diabetes associated with ADT? *Nat Clin Pract Urol*. 2008;5:306-307.

38. Beydoun N, Bucci JA, Chin YS, *et al*. Prospective study of exercise intervention in prostate cancer patients on androgen deprivation therapy. *J Med Imaging Radiat Oncol*. 2014;58:369-376.

39. Newton RU, Taaffe DR, Spry N, *et al*. Can exercise ameliorate treatment toxicity during the initial phase of testosterone deprivation in prostate cancer patients? Is this more effective than delayed rehabilitation? *BMC Cancer*. 2012;12:432-440.

40. Galvão DA, Taaffe DR, Spry N, *et al*. Acute versus chronic exposure to androgen suppression for prostate cancer: Impact on the exercise response. *J Urol*. 2011;186:1291-1297.

41. Cormie P, Galvão DA, Spry N, *et al*. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: A randomized controlled trial. *BJU Int*. 2014;115:256-266.

42. Garland SN, Johnson B, Palmer C, *et al*. Physical activity and telomere length in early stage breast cancer survivors. *Breast Cancer Res*. 2014;16:413-422.

43. Shammas MA. Telomeres, lifestyle, cancer, and aging. *Curr Opin Clin Nutr Metab Care*. 2011;14:28–34.

44. Ludlow AT, Zimmerman JB, Witkowski S, *et al*. Relationship between Physical Activity Level, Telomere Length, and Telomerase Activity. *Med Sci Sports Exerc*. 2008;40:1764–1771.

45. Heber S, Volf I. Effects of physical (in)activity on platelet function. *Biomed Res Int*. 2015;14:1-11.

46. Sharma D, Brummel-Ziedins KE, Bouchard BA, *et al*. Platelets in tumor progression: A host factor that offers multiple potential targets in the treatment of cancer. *J Cell Physiol*. 2014;229:1005-1015.

47. Egan K, Cooke N, Kenny D. Living in shear: Platelets protect cancer cells from shear induced damage. *Clin Exp Metastasis*. 2014;31:697-704.

48. Wang J, Lu D, Mao D, *et al*. Mechanomics: An emerging field between biology and biomechanics. *Protein Cell*. 2014;5:518-531.

49. Lynch ME, Fischbach C. Biomechanical forces in the skeleton and their relevance to bone metastasis: Biology and engineering considerations. *Adv Drug Deliv Rev*. 2014;79-80:119-134.

50. 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.

51. Chen X, Goh JCH, Teoh SH, *et al*. Localized sclerotic bone response demonstrated reduced nanomechanical creep properties. *J Mech Behav Biomed Mater*. 2013;17:198-208

52. Lecouvet FE, Talbot JN, Messiou C, *et al*. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer*. 2014;50:2519-2531.

53. Shah LM, Salzman KL. Imaging of Spinal Metastatic Disease. *Int J Surg Oncol*. 2011;2011:769753

54. Tombal B, Lecouvet F. Modern detection of Prostate Cancer's Bone Metastasis: Is the bone scan era over? *Adv Urol*. 2012;2012:893193

55. Dunn LK, Mohammad KS, Fournier PG, *et al*. Hypoxia and TGF-β Drive Breast Cancer Bone Metastases through Parallel Signaling Pathways in Tumor Cells and the Bone Microenvironment. *PLoS One*. 2009;4:e6896.

56. Hart NH, Nimphius S, Spiteri T, *et al*. Segmental musculoskeletal examinations using dual-energy X-ray absorptiometry (DXA): Positioning and analysis considerations. *J Sport Sci Med*. 2015;14:620-626

57. Hologic. QDR for Windows XP Reference Manual. *Hologic Inc*. 2014

58. Hart NH, Nimphius S, Weber J, *et al*. Musculoskeletal asymmetry in football athletes: A product of limb function over time. *Med Ex Sport Sci*. 2016;15:1379-1387.

59. 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;14:67-77.

60. McGill SM. Low back stability: from formal description to issues for performance and rehabilitation. *Exer Sport Sci Rev*. 2001;29:26–31.

61. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. 2011;2:109-112.

62. Hopkins WG. A scale of magnitudes for effect statistics. *SportScience*. 2002. http://www.sportsci.org/resource/stats/effectmag.html. Accessed 15 Jan 2016.

63. Jones LW, Alfano CM. Exercise-oncology research: Past, present, and future. *Acta Oncol*. 2013;52:195-215

64. Pedersen L, Christensen JF, Hojman P. Effects of Exercise on Tumor Physiology and Metabolism. *Cancer J*. 2015;21:111-116

65. Secomb TW, Alberding JP, Hsu R, *et al*. Angiogenesis: An adaptive dynamic biological patterning problem. *PLoS Comput Biol*. 2013;9:e1002983.

66. Siemann DW, Horsman MR. Modulation of the tumor vasculature and oxygenation to improve therapy. *Pharmacol Ther*. 2015;153:107-124.

67. Ergun M, Eyigor S, Karaca B, *et al*. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *Eur J Cancer Care*. 2013;22:626–637

68. Galvão DA, Taaffe DR, Spry N, *et al*. Enhancing Active Surveillance for Men with Prostate Cancer: The Potential Role of Exercise Medicine. *Nat Rev Urol*. 2016:13:258-265.

LEGEND OF FIGURES

Figure 1. Schematic overview of the study protocol. MRI = Magnetic Resonance Imaging; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; 1RM = One Repetition Maximum.

LEGEND OF TABLES

Table 1. Schedule of assessments at baseline, on-trial and post-intervention

Table 2. Weekly distribution of testing, M3EP and SIT exercise sessions across the exercise intervention

Table 3. Modular multi-modal exercise program (M3EP) for patients with bone metastases [9,10]

LEGEND OF SUPPLEMENTARY FILES

Supplementary File 1. Floor-based, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for varying physical capabilities and training progression rates.

Supplementary File 2. Seated and standing, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for patients unable to perform floor-based exercises.

Table 1. Schedule of assessments at baseline and post-intervention.

Measures	Baseline	Post-Intervention
Tumour Morphology – (off-site)		
- MRI Scan: T1-Axial	X	X
Tumour Biomarkers		
- Blood: HIF-1α, TGF-β	X	X
Anthropometry		
- Height (cm)	X	
- Weight (kg)	X	X
- Waist Circumference (cm)	X	X
- Hip Circumference (cm)	X	X
- Femoral Length (mm)	X	
- Tibial Length (mm)	X	
- Body Mass Index (kg/m^2)	X	X
- Waist-to-hip ratio	X	X
Body Composition		
- DXA Scans: Whole-body, Spinal, Hip	X	X
- pQCT Scans: Femoral, Tibial	X	X
Physical Assessments		
- NeuroCom Balance Test	X	X
- 1RM Strength Test (Leg Extension)	X	X
- 400m Walk Test	X	X
- Timed Up and Go Test	X	X
Other Biomarkers – (off-site)		
- Blood: P1NP, ALP, CRP, Fasting Glucose and Lipids, PSA	X	X
- Urine: NTx	X	X
Questionnaires		
- Demographic and Health History	X	
- Concomitant Medications	X	X
- Health-related Quality of Life (SF-36)	X	X
- Cancer-specific Quality of Life (EORTC: QLQ30, PR25)	X	X
- Brief Symptom Index (BSI-18)	X	X
- Insomnia Severity Index (ISI)	X	X
- Godin Leisure-time Exercise	X	X
Safety and Tolerance – (Intervention Arm)		
- Adverse Events	At each exercise session	
- Bone Pain Levels	At each exercise session	
- Fatigue Levels	At each exercise session	
- Rating of Perceived Exertion	At each exercise session	
Adherence and Compliance – (Intervention Arm)		
- Clinic Exercise Record Sheet (Prescribed versus Actual)	At each exercise session	
- Home Isometric Exercise Record Sheet (Prescribed versus Actual)	At each exercise session	
Safety – (Control Arm)		
- Adverse Events	Tri-weekly telephone call	

Note: HIF-1α = Hypoxia-Inducible Factor 1-alpha; TGF-β = Transformation Growth-like Factor beta; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; P1NP = amino-terminal propeptide of type 1 procollagen; NTx = amino-terminal collagen type-1 telopeptide; ALP = Alkaline Phosphate; CRP = C-reactive protein; PSA = Prostate-Specific Antigen; SF-36 = Short Form-36; EORTC = European Organisation for Research and Treatment of Cancer.

Table 2. Weekly distribution exercise testing and training sessions across the intervention.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 0	Baseline Testing						
Week 1 to Week 12	SIT M3EP	SIT	SIT M3EP	SIT	SIT M3EP	REST	REST
Week 13	Post-Intervention Testing						

Note: SIT = Spinal Isometric Training (15 minutes); M3EP = Modular Multi-Modal Exercise Program (60 minutes). Clinic exercise sessions occur on Monday, Wednesday and Friday; home-based spinal isometric exercise sessions occur on Tuesday and Thursday. Spinal isometric exercises are provided at the start of clinic exercise sessions (following a general warm-up).

Table 3. Modular multi-modal exercise program (M3EP) for patients with bone metastases [9,10]

	Resistance			Aerobic		Flexibility
Metastases Site	**Upper**	**Trunk**	**Lower**	**WB**	**NWB**	**Static**
Pelvis	√	√	√**		√	√
Lumbar Spine	√		√		√	√***
Thoracic Spine / Ribs	√*		√	√	√	√***
Proximal Femur	√	√	√**		√	√
All Regions	√*		√**		√	√***

Note: √ = 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.

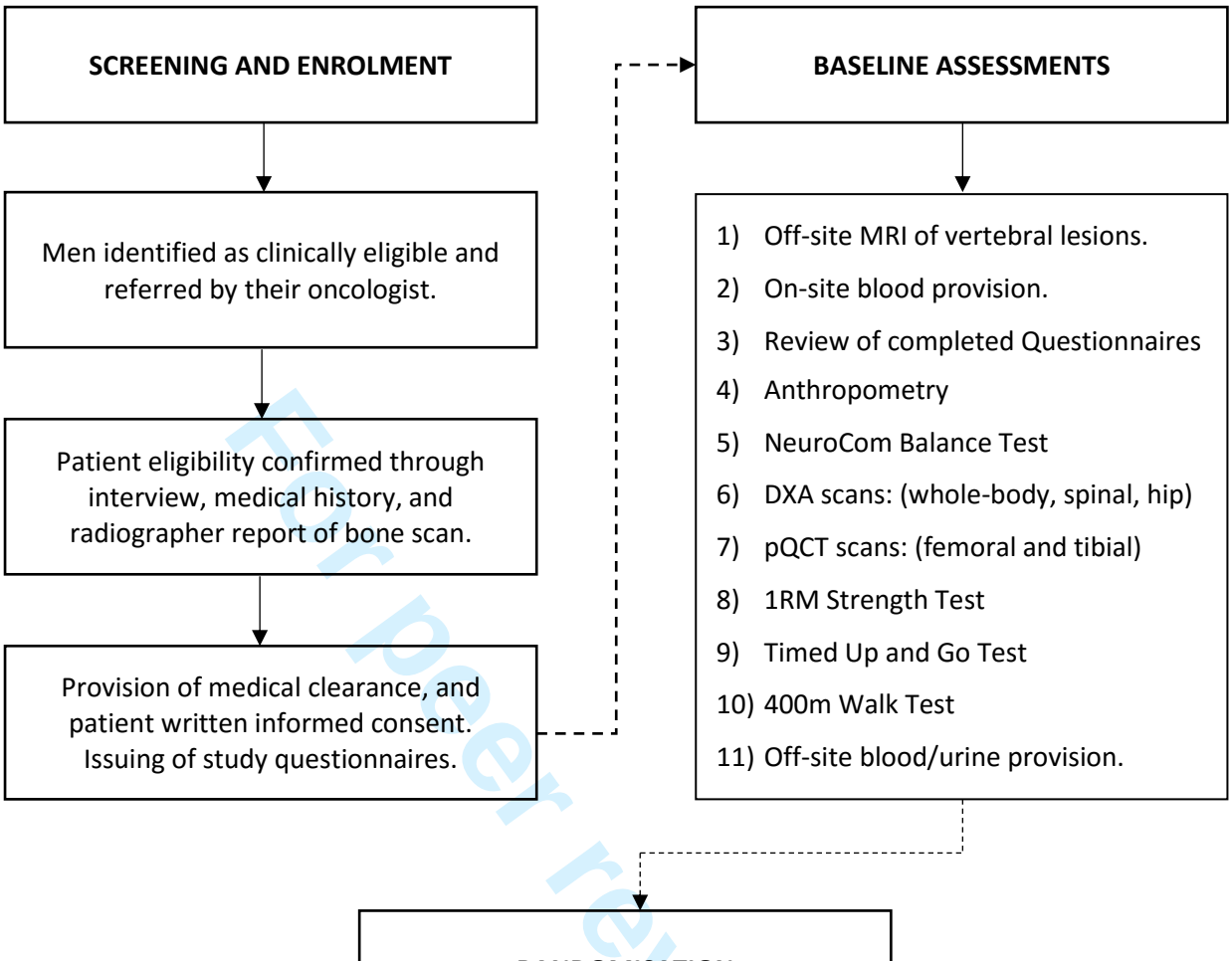


Figure 1. Schematic overview of the study protocol. MRI = Magnetic Resonance Imaging; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; 1RM = One Repetition Maximum.

Supplementary Table 1. Floor-based, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for varying physical capabilities and training progression rates.

Exercise	Instruction
Abdominal Brace #1: - Single Leg Lift	**Start position:** Supine on floor with arms by their side, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise one foot off the floor until shank is parallel to the floor. Hold for 10 seconds. Lower foot to floor and repeat on the other limb. **Volume:** Perform 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Abdominal Brace #2: - Double Leg Lift	**Start position:** Supine on floor with arms by their side, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise both feet off the floor until both shanks are parallel to the floor. Hold for 10 seconds. Lower both feet to floor. **Volume:** Perform 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Abdominal Brace #3: - Leg Fall Out	**Start position:** Supine on floor with hands resting on hips, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly allow one leg to rotate outward towards the floor by relaxing the adductor muscles. Do not allow rotation at the spine or pelvis. Repeat on opposite leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
Abdominal Brace #4: - Foot Slide	**Start position:** Supine on floor with hands resting on hips, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly slide one leg out (extending at the hip and knee) and back along the floor. Repeat on opposite leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
'All Fours' Position #1: - Hip Hinges	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly flex at the hips and knees, moving backward. Patient should sit into this position so that their buttocks touches their heels while arms remain fixed. Return to start position. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
'All Fours' Position #2: - Arm Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one arm off the ground. Maintain balance by holding a neutral and firm spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on alternate arm. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
'All Fours' Position #3: - Leg Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one leg off the ground. Maintain balance by holding a neutral and firm spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on alternate leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
'All Fours' Position #4: - Arm & Leg Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one arm and the opposite leg off the ground. Maintain balance by holding a neutral spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on the alternate arm/leg combination. **Volume:** 2-4 sets of 8-12 repetitions. **Rest:** 30 seconds between sets.
Bridge #1: - Full Hip Extension	**Start position:** Supine on floor with hands by their side, knees bent and feet on the floor. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Pause for 5 seconds in this position prior to slowly lowering hips back to the floor. **Volume:** 2-4 sets of 8-12 repetitions.

	Rest: 60 seconds between sets.
Bridge #2: - Single Hip Extension	**Start position:** Supine on floor with hands by their side, knees bent and feet on the floor. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Once in this position, slowly extend and straighten one leg. Slowly return extended leg back to the floor before also lowering the hips back to the floor. Alternate between legs. **Volume:** 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Bridge #3: - Side Bridges	**Start position:** Lying on their side, with arm abducted, resting on their forearm. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Maintain knee contact with the floor. Hold this position for up to 90 seconds (or as long as achievable without compromising technique). Alternate sides. This can be progressed by performing this exercise with legs fully extended (resting on forearm and feet). **Volume:** Hold for 10- 90 seconds. Repeat 2-4 times. **Rest:** 60 seconds between sets.
Bridge #4: - Prone Planks	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Straighten legs while arms remain outstretched, ensuring abdominals remain braced. Hold this position for up to 90 seconds (or as long as achievable without compromising technique). This can be progressed by performing this exercise while resting on forearms. **Volume:** Hold for 10-90 seconds. Repeat 2-4 times. **Rest:** 60 seconds between sets.

Note: Always maintain neutral spine and control pelvic tilt. Spine must be supported through abdominal bracing to ensure safe delivery of these exercises [60]. Practitioners must always be cautious and observant to ensure correct technique and posture is upheld. Patients with cervical bone metastases are contraindicated for Bridge #1 or Bridge #2 and should not perform these two exercises.

Supplementary Table 2. Seated and standing, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for patients unable to perform floor-based exercises.

Exercise	Instruction
Seated Exercise #1 - Marching	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one knee up as high as flexibility allows (while maintaining upright posture). Pause at the top for 2 seconds and lower back down. Repeat with the opposite limb. Only one foot should be on the ground at a time to simulate slow paced marching. Focus on patient posture and trunk stability to ensure proper muscle activation. To increase difficulty, **Volume:** Perform 2-4 sets of 8-12 repetitions (each leg). **Rest:** 30 seconds between sets.
Seated Exercise #2 - Leg Extension	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise one foot off the floor to straighten the leg (until the shank is parallel to the floor). Hold for 5 seconds. Lower the foot to the floor. Repeat on the other leg. To increase difficulty, if seated on a stable bench (or chair), patient can use both legs simultaneously. Alternatively, patients can perform single-leg extensions against theraband resistance or while seated on a fit-ball. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** Perform 2-4 sets of 8-12 repetitions (each leg). **Rest:** 30 seconds between sets.
Seated Exercise #3 - Theraband Row	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Wrap an elastic band around a fixed object at chest level in front of the patient. Use a band which provides a mild resistance. With arms fully extended, slowly pull the band towards the chest, keeping the elbows low and close to the body, until the elbows bend to approximately 90 degrees. Hold position for 5 seconds. Slowly return to the start position. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
Hybrid Exercise #1 - Sit-to-Stand	**Start position:** Seated on a bench or chair; back straight with arms crossed over. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Stand up from the seated position. Once fully upright, return slowly to a seated position. Aim is to perform this exercise without using arms for assistance (if possible). Avoid this exercise if patient has knee pathology. Focus on patient posture and **movement quality** to ensure proper muscle activation and safe performance of this exercise. **Volume:** 2-4 sets of 8 repetitions **Rest:** 60 seconds between sets.
Standing Exercise #1 - Wall Push-Up	**Start position:** Standing. Place hands on wall at shoulder height, with arms extended. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly lower their body and hips towards the wall by bending at the elbows in a controlled manner. Once their face is near the wall, hold for 5 seconds and then slowly push against the wall to extend the arms and return back to starting position. Focus on patient posture and trunk stability to ensure proper muscle activation. To increase difficulty, patient can increase angle against the wall. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
Standing Exercise #2 - Wall Plank	**Start position:** Standing. Leaning forward on forearms against a wall. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). While leaning on forearms against the wall, slowly move feet backward to desired angle between the body and wall. Focus on placing body weight onto forearms while keeping trunk muscle engaged, torso straight with neutral spine. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.

Standing Exercise #3 - Theraband Row	**Start position:** Standing; back straight, split-stance (one foot forward, one foot back). **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Wrap an elastic band around a fixed object at chest level in front of the patient. Use a band which provides a mild resistance. With arms fully extended, slowly pull the band towards the chest, keeping the elbows low and close to the body, until the elbows bend to approximately 90 degrees. Hold position for 5 seconds. Slowly return to the start position. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.

Note: Always maintain an upright trunk (straight back) with neutral spine and control pelvic position during all exercises. Spine must be supported through abdominal bracing to ensure safe delivery of these exercises [60]. Practitioners must always be cautious and observant to ensure correct technique and posture is upheld.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014458.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2017
Complete List of Authors:	Hart, Nicolas; Edith Cowan University, Exercise Medicine Research Institute Newton, Robert; Edith Cowan University, Exercise Medicine Research Institute Spry, Nigel; Sir Charles Gairdner Hospital, Department of Radiation Oncology; Edith Cowan University, Exercise Medicine Research Institute Taaffe, Dennis; Edith Cowan University, Exercise Medicine Research Institute Chambers, Suzanne; Griffiths University, Menzies Health Institute; Edith Cowan University, Exercise Medicine Research Institute Feeney, Kynan; Edith Cowan University, Exercise Medicine Research Institute; St John of God Hospital, Department of Medical Oncology Joseph, David; Sir Charles Gairdner Hospital, Department of Radiation Oncology; Edith Cowan University, Exercise Medicine Research Institute Redfern, Andrew; Fiona Stanley Hospital, Department of Medical Oncology; University of Western Australia, School of Medicine and Pharmacology Ferguson, Tom; Fiona Stanley Hospital, Department of Medical Oncology Galvão, Daniel; Edith Cowan University, Exercise Medicine Research Institute
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Sports and exercise medicine, Rehabilitation medicine
Keywords:	tumour biology, tumour activity, resistance training, isometric training, aerobic exercise

Can exercise suppress tumour growth in advanced prostate cancer patients with sclerotic bone metastases? A randomised, controlled study protocol examining feasibility, safety and efficacy.

Nicolas H. Hart, PhD [1]; Robert U. Newton, PhD [1]; Nigel A. Spry, MD PhD [1,2,3]; Dennis R. Taaffe, PhD DSc MPH [1]; Suzanne K. Chambers, PhD [1,4]; Kynan T. Feeney, MD MPH [1,5,6]; David J. Joseph, MD [1,2]; Andrew D. Redfern, MD, PhD [7,8]; Tom Ferguson, MD [7]; Daniel A. Galvão, PhD [1]

[1] Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia
[2] Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia
[3] Department of Radiation Oncology, Genesis CancerCare, Perth, WA, Australia
[4] Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia
[5] Department of Medical Oncology, St John of God Hospital, Perth, WA, Australia
[6] School of Medicine, University of Notre Dame Australia, Perth, WA, Australia
[7] Department of Medical Oncology, Fiona Stanley Hospital, Perth, WA, Australia
[8] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

Running Title: *Exercise and tumour suppression.*

Corresponding Author:
Dr. Nicolas H. Hart – PhD, AES, CSCS, ESSAM.
Exercise Medicine Research Institute
Edith Cowan University, 270 Joondalup Drive, Joondalup
Perth, Western Australia, Australia – 6027.
Ph: +61 8 6304 3436
Fax: +61 8 6304 2499
Email: n.hart@ecu.edu.au

Key Words: tumour biology; tumour activity; isometric; resistance; aerobic; flexibility.

ABSTRACT

Introduction: Exercise may positively alter tumour biology through numerous modulatory and regulatory mechanisms in response to a variety of modes and dosages, evidenced in pre-clinical models to date. Specifically, localised and systemic biochemical alterations produced during and following exercise may suppress tumour formation, growth and distribution by virtue of altered epigenetics and endocrine-paracrine activity. Given the impressive ability of targeted mechanical loading to interfere with metastasis-driven tumour formation in human osteolytic tumour cells, it is of equal interest to determine whether a similar effect is observed in sclerotic tumour cells. The study aims to 1) establish the feasibility and safety of a combined modular multi-modal exercise program with spinal isometric training in advanced prostate cancer patients with sclerotic bone metastases, and 2) examine whether targeted and supervised exercise can suppress sclerotic tumour growth and activity in spinal metastases in humans.

Methods and Analysis: A single-blinded, two-armed, randomised, controlled and explorative phase 1 clinical trial combining spinal isometric training with a modular multi-modal exercise program in 40 men with advanced prostate cancer and stable sclerotic spinal metastases. Participants will be randomly assigned to (1) the exercise intervention or (2) usual medical care. The intervention arm will receive a 3-month, supervised and individually tailored modular multi-modal exercise program with spinal isometric training. Primary end-points (feasibility and safety) and secondary end-points (tumour morphology; biomarker activity; anthropometry; musculoskeletal health; adiposity; physical function; quality of life; anxiety; distress; fatigue; insomnia; physical activity levels) will be measured at baseline and following the intervention. Statistical analyses will include descriptive characteristics, t-tests, effect sizes and two-way (group x time) repeated measures ANOVA (or analysis of covariance) to examine differences between groups over time. The data-set will be primarily examined using an intention-to-treat approach with multiple imputations, followed by a secondary sensitivity analysis to ensure data robustness using a complete cases approach.

Ethics and Dissemination: Ethics approval was obtained from the Human Research Ethics Committee (HREC) of Edith Cowan University and the Sir Charles Gairdner and Osborne Park Health Care Group. If proven to be feasible and safe, this study will form the basis of future phase II and III trials in human patients with advanced cancer. To reach a maximum number of clinicians, practitioners, patients and scientists, outcomes will be disseminated through national and international clinical, conference and patient presentations, as well as publication in high-impact, peer-reviewed academic journals.

Trial Registration: ACTRN-12616000179437

STRENGTHS AND LIMITATIONS

- This is a novel, phase I randomised controlled trial in humans exploring the preliminary effects of targeted exercise on tumour morphology and circulating metastatic tumour biomarkers using a sclerotic skeletal metastases model in prostate cancer patients.
- The study is principally aimed at establishing feasibility and safety, and may lack statistical power or a suitable length of intervention to determine the efficacy of exercise on tumour biology and metastatic tumour biomarkers.

INTRODUCTION

Bone is the most common location for metastatic prostate carcinoma, with skeletal lesions identified in over 80% of advanced prostate cancer patients[1-5]. These lesions predominantly present as sclerotic (osteoblastic) and primarily reside in the axial skeleton (spine, pelvis or ribs)[6-8], presenting a considerable challenge for practitioners to deliver exercise interventions to this population[9,10]. In particular, advanced cancer patients have historically been excluded from exercise intervention studies and community-based supervised exercise programs due to potential adverse skeletal events. Consequently, advanced cancer patients often fail to receive the crucial benefits of exercise in the management their disease; that is, to reduce treatment toxicities, delay disease progression and increase survival through neo-adjuvant, adjuvant, synergistic and targeted applications. Clinically, bone metastases present as a major concern with patients experiencing severe bone pain, increased risk of skeletal complications, spinal compression, hypercalcaemia and decreased physical function and quality of life[9-13]. Subsequently, patients with metastatic bone disease experience significant morbidity with many barriers to exercise participation, thus strategies to safely and effectively reduce the burden of bone metastatic disease have a high degree of clinical importance.

Despite the unequivocal benefits of exercise for cancer patients[14-25], fear of adverse skeletal events has led to reduced uptake by patients, and reduced referrals to exercise programs by clinicians[9,10,18]; a cycle which exacerbates musculoskeletal fragility and tumour progression. In recent times, Galvão and colleagues[9,10,21] designed a modular, multi-modal exercise program (M3EP) to provide this population with safe and effective exercise modified to avoid direct loading of lesion sites; the first of its kind in exercise oncology. Preliminary findings have been promising, with exercise shown to be well tolerated (safe and efficacious); delivering clear improvements in physical function, physical activity levels and lean mass in these patients[10,21].

However, it is not yet known whether direct loading of lesion sites in bone metastases is safe to deliver, or therapeutically advantageous in providing adjuvant, synergistic or independent health benefits or tumoral modulations in advanced prostate cancer patients.

Exercise positively alters tumour biology via numerous mechanisms in response to a variety of modes and dosages[26-33]. Specifically, exercise regulates endocrine-paracrine activity, immune system function, blood glucose levels, blood cholesterol levels, insulin response and body composition[34-41]; whilst epigenetically modulating tumour cell proliferation, telomere length, telomere enzyme activity, tumour vascularity, oxidative stress capacity, platelet cloaking and platelet adhesion[26-33,42-47]. Although these regulatory and modulatory outcomes interact, the ability to suppress tumour formation, growth and spread by virtue of altered epigenetics and endocrine-paracrine activity through exercise is of particular interest. This emerging field of mechanomics in exercise oncology (biological alterations driven from biomechanical stimuli)[48-51] presents practitioners with a unique opportunity to potentially suppress metastatic prostate carcinoma in bone through targeted exercise interventions.

Direct loading of animal metastatic bones containing human breast cancer tumour cells supports this new direction, successfully interfering with metastasis-driven tumour formation[50] by delivering suppressive localised modulatory changes to the tumour microenvironment, while preserving bone material, structure and strength[49,50]. Given the impressive ability of mechanical loading to epigenetically interfere with metastasis-driven tumour formation in osteolytic tumour cells, it is of equal interest to determine whether mechanical loading is also able to alter metastasis-driven tumour formation in sclerotic tumour cells. This may also prove to be an effective adjuvant intervention to alleviate bone pain, preserve musculoskeletal strength, and suppress sclerotic tumour expansion. To our knowledge, no studies have directly targeted skeletal metastases in advanced cancer patients through controlled, localised exercise

programs in order to plausibly modulate tumour biology and suppress tumour growth in humans; 'nor are we aware of any studies that have specifically established the feasibility or safety of loading skeletal sites with sclerotic bone metastases in advanced prostate cancer patients.

The aim of this study is to 1) examine whether a modular multi-modal exercise program with spinal isometric training is feasible and safe in advanced prostate cancer patients with sclerotic bone metastases in order to produce targeted and localised adaptations surrounding spinal lesions, and 2) examine the preliminary efficacy of targeted and supervised exercise to suppress sclerotic tumour growth and activity in spinal metastases in humans. We hypothesise that the exercise program will be feasible and safe to deliver to advanced prostate cancer patients; and that the exercise program will help reduce the rate of sclerotic tumour progression. In addition, we also hypothesise the exercise program will alleviate bone pain; not increase the incidence of skeletal fractures; act to preserve muscle and bone; improve physical fitness and functional ability; reduce cancer-related fatigue and increase quality of life and psychosocial wellbeing. The outcomes of this trial will be used to improve clinical knowledge pertaining to exercise prescription for advanced cancer patients with metastatic prostate carcinoma, specifically promoting isometric loading of bones with sclerotic lesions. The outcomes of this trial will also be used to establish preliminary efficacy of tumour suppression through exercise, thereby informing phase II and III clinical trials to help establish new clinical exercise guidelines in this high risk and unique population.

METHODS AND ANALYSIS

Study Design

This is a single-blinded (investigators blinded to group allocation), two-armed, randomised and controlled (exercise versus usual care) explorative phase 1 clinical trial which

will examine the feasibility, safety and preliminary efficacy of combining spinal isometric training with a modulatory, multi-modal exercise program (M3EP-SIT) in men with advanced prostate cancer and sclerotic spinal bone metastases. The exercise group (intervention arm) will receive an individually tailored and supervised 3-month (12 weeks) exercise program involving resistance, aerobic, flexibility and isometric exercises in addition to usual medical care. The control group will receive usual medical care during this time and will be asked not to change their baseline levels of physical activity. Following the trial, the control group will be offered the same exercise program if the intervention is deemed to be safe and feasible. This procedure has been shown to be an effective strategy to minimise study contamination, patient withdrawals or loss of patients to follow-up in prior exercise oncology trials[9,24,39].

Recruitment

Patients will be recruited by invitation of their cancer specialist (urologist, radiation oncologist or medical oncologist) who will provide clinically eligible patients with a study information sheet and refer these patients to a study coordinator. If patients are interested in participation, and their eligibility is confirmed, they will receive an informed consent document to read and sign in the presence of a study investigator and clinical research coordinator before undertaking baseline measurements prior to randomisation (Figure 1).

Randomisation

Patients will be randomly allocated in a ratio of 1:1 to the two study arms: exercise or usual care, stratified by age (≤70 years, >70 years) and time since completion of chemotherapy, radiotherapy to spinal metastases or change in hormone therapy (<3 months, ≥3 months) for approximate balance between groups in order to mitigate confounding factors pertaining to variations due to ageing (i.e. differences in physical function, sarcopenia, osteopenia and osteoporosis) and to account for variations in the treatment and wash-out effect of any recent completions of chemotherapy and radiotherapy, or changes in hormone therapy (i.e. if

progressed to second-line anti-androgen agents). All patients will be required to be on androgen deprivation therapy (ADT) prior to, and during this study, as per standard of care for this patient population. A research officer with no patient contact will be responsible for randomisation of patient's into either group by using a computer random assignment programme. Study investigators and exercise physiologists conducting testing procedures will be blinded to group allocation. Only exercise physiologists not in the research team will be permitted to deliver the exercise intervention to participants in order to maintain integrity of the blinding process.

Participants

Forty men (20 subjects per arm) with prostate cancer and stable bone metastases in cervical, thoracic and/or lumbar vertebrae, who have not engaged in regular exercise (i.e. undertaking structured aerobic or resistance training two or more times per week) within the past 3 months will serve as participants. Due to the novelty of this explorative phase 1 clinical trial with a primary end-point to establish feasibility and safety; our sample size was chosen based on prior pre-clinical animal studies[26,30,32,50], human pilot studies[31,33] and consideration of recruitment ability for advanced prostate cancer patients with bone metastases. In addition, to demonstrate a meaningful difference (effect size ≥1.0; 80% power; alpha level of 0.05 [two-tailed]) for most secondary endpoints, 16 subjects per group would be required. To account for up to a 25% attrition rate, 40 subjects will be randomised evenly to each study arm (Exercise: n=20; Control: n=20) to assist with establishing preliminary efficacy of secondary end-points; and to form the basis of sophisticated power calculations for future Phase II and III randomised controlled trials.

Patients will be excluded from this trial if they have commenced chemotherapy; if they are receiving radiotherapy for any spinal bone metastases; if they have commenced or changed hormone therapy within 3 months of enrolment; or are currently receiving any other

experimental treatments or non-approved therapies. Patients are permitted to receive radiotherapy for non-spinal bone metastases only while enrolled in this trial. Patients require medical clearance prior to enrolment, therefore must achieve an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 1; and must not have any acute illness, significant bone pain, or cardiovascular or neurological disorders that could inhibit exercise participation. All participants must provide written informed consent prior to participation. The protocol has been approved by the Human Research Ethics Committee of Edith Cowan University (ID: 13399 HART and 14146 HART); and Sir Charles Gairdner and Osborne Park Health Care Group (ID: 2016-118). This trial is also registered with the Australia and New Zealand Clinical Trails Register (ANZCTR), Trial ID: ACTRN-12616000179437. All data relevant to the study will be kept on password-encrypted computers accessible by study investigators situated at the Exercise Medicine Research Institute (Perth, WA, Australia).

Measurements

Primary and secondary endpoints will be assessed at baseline (Week 0), post-intervention (Week 13) and through-out the 12-week on-trial period (Table 1).

Primary Endpoint

Feasibility

Feasibility will be quantified through a series of multi-item categories including patient recruitment and trial completion; patient safety; program tolerance; program adherence and program compliance (Table 2). Program safety will be assessed by recording the incidence and severity of adverse events and/or skeletal complications through-out the on-trial period for intervention and control arms. Skeletal complications include heightened pain at sites of bone metastases and/or pathological skeletal fractures. The nature, severity and impact of bone pain will be examined using the FACIT Bone Pain questionnaire at baseline and post-intervention.

Program tolerance, adherence and compliance will be assessed for the intervention arm only. Specifically, program tolerance will be quantified by measuring pre-sessional bone pain and fatigue at each exercise session through visual analog scales (VAS, 0-10) and by recording sessional rating of perceived exertion (RPE; Borg Scale, 0-10) and sessional tolerance (VAS, 0-7) after each exercise session.

Program adherence and compliance will be assessed using an exercise diary completed by the patient at all clinic-based and home-based exercise sessions to record the volume of resistance training (weight lifted [kg], sets and repetitions), aerobic training (intensity [level], duration [minutes], speed [revolutions-per-minute], heart rate [maximum and average] and rating of perceived exertion) flexibility training (repetitions) and isometric training (repetitions and hold duration) completed. This data will be compared to the prescribed and individualised exercise program provided to each patient in order to establish program adherence (completed versus missed sessions) and compliance (prescribed versus actual exercise completed for each training modality [resistance, aerobic, flexibility and isometric]).

Secondary Endpoints

Tumour Morphology

Tumour morphology will be measured using axial T1-weighted magnetic resonance imaging (MRI) scans (1.5T, Magnetom Essenza, Siemens, Victoria, Australia) in locations where sclerotic lesions have been identified in patients with bone metastases at either thoracic or lumbar spinal regions[52-54]. Location of metastatic lesions will be previously recorded through bone scans provided by the patient's primary oncologist prior to referral to this study. All scans will be performed on the same MRI machine by the same radiologist using a standardised sequence and routine for scout and primary acquisitions. Specifically, spinal bone metastases will be identified and confirmed using three preliminary axial scout scans in the sagittal plane

to view cervical, thoracic and lumbar regions respectively (T2-weighted; imaging frequency = 63.66 Hz; slice thickness = 3.0 - 4.0 mm; spacing between slices = 3.6 - 6.0 mm; echo train length = 16 - 21; flip angle = 140 - 150 °; acquisition matrices = 256\0\0\192 [cervical], 448\0\0\358 [thoracic], 320\0\0\320 [lumbar]).

Primary acquisition for each affected vertebrae will be performed in the transverse plane, capturing the vertebrae above and below to produce an image with three vertebrae in total (T1-weighted; imaging frequency = 63.66 Hz; slice thickness = 4.0 mm; space between slices = 4.2 mm; echo train length = 3; flip angle = 150 °; acquisition matrix = 384\0\0\307). Following acquisition, tumour morphology (volume [mm^3], intensity [W/sr]) will be examined for each slice using ITK-Snap (Version 3.6.0) image analysis software[55] (Figure 2). All images will be examined at the conclusion of the study by two independent researchers for consistency in analysis, and to establish intra-rater and inter-rater reliability coefficients.

Biomarkers

Metastatic tumour biomarkers, HIF-1α and TGF-β will be examined through unfasted serological samples acquired at baseline and post-intervention testing sessions to measure hypoxic activity and transformation-growth activity respectively; identified as key synergistic drivers of metastatic tumour progression[56]. Fasted serological and first-void urianalytical samples will be collected within 48 hours of baseline and post-intervention testing sessions to measure bone metabolic activity and systemic inflammation. Specifically, bone formation marker, amino-terminal propeptide of type 1 procollagen (P1NP); bone resorption marker, amino-terminal collagen type-I telopeptide (NTx); bone disorder marker, alkaline phosphate (ALP); inflammation marker, C-reactive protein (CRP); and fasting glucose and lipid profiles will be examined. Prostate specific antigen (PSA) will also be assessed. All fasted serological and first-void urianalytical biomarkers will be collected in the morning, and assessed by the

same accredited laboratory (St John of God Hospital, Pathology Laboratory, Perth, Western Australia).

Anthropometry

Stature will be recorded to the nearest 0.1 cm using a wall-mounted stadiometer (Model 222, Seca, Hamburg, DE), with body mass recorded to the nearest 0.1 kg using an electronic scale (AE Adams CPW Plus-200, Adam Equipment Inc., CT, USA). Waist and hip circumferences are defined as the mid-point between the 10th rib and iliac crest; and the level of the greater trochanter, respectively, with the waist-to-hip ratio calculated. Waist circumference and hip circumference will be measured to the nearest 0.1 cm using a constant-tension, retractable measuring tape (Model 4414, Tech-Med Services, NY, USA). Stature, waist circumference and hip circumference will be performed in triplicate for each participant, with the average of each variable retained for analysis.

Musculoskeletal Health

Whole-body, segmental (axial, appendicular) and regional (spinal, hip, proximal femur) scans will be performed to examine bone area (BA), areal bone mineral content (aBMC), areal bone mineral density (aBMD) and lean mass using Dual-energy X-ray Absorptiometry (DXA; Hologic Discovery A, Waltham, MA). Whole-body and appendicular segmentations will be analysed in accordance with Hart and colleagues[57]. Regional analyses (lumbar spine, total hip, femoral neck, trochanter, Wards triangle) will be performed in accordance with Hologic's manufacturer specifications[58].

Appendicular, non-lesion control sites will be scanned to quantify bone material, structure and strength using peripheral Quantitative Computed Tomography (pQCT; XCT-3000, Stratec, Pzochienheim, Germany). Specifically trabecular, cortical, marrow and total volumetric density (Tb.vBMD, Ct.vBMD, Ma.vBMD, Tt.vBMD); trabecular, cortical, marrow

and total cross-sectional area (Tb.Ar, Ct.Ar, Ma.Ar, Tt.Ar); cortical thickness (Ct.Th); stress-strain index (SSIPOL); absolute fracture load (FL.Ab) and relative fracture load (FL.Rel) of the left Femur (4% and 33% slices) and left Tibia (4%, 14%, 38% and 66% slices) will be measured and analysed in accordance with Hart and colleagues[59]. Muscle cross-sectional area (Mu.Ar) will also be quantified.

Adiposity

Whole-body, segmental and central subcutaneous adipose tissue (fat mass); central visceral adipose tissue (VAT; area, mass and volume); and android to gynoid ratio will be measured using DXA. Whole-body and appendicular segmentations will be generated in accordance with Hart and Colleagues[57]. Fat area (Fa.Ar) and muscle density (Mu.Den) of the thigh and shank segments will be measured using pQCT[59], as an indication of subcutaneous and intramuscular fat infiltration, respectively.

Objective Measures of Physical Function

Muscle strength, aerobic capacity and physical function will be measured through a series of assessments. Muscle strength will be measured using the one repetition maximum (1RM) test for the leg extension exercise. This exercise was chosen as it can be safely performed by all patients included in this study. The 400m walk test and Timed Up and Go test will be used as measures for aerobic capacity and physical function respectively. In addition, patients will also undergo a comprehensive balance test (NeuroCom Smart Balance Master, Natus Medical Inc., USA).

Quality of Life, Anxiety, Distress, Fatigue, Insomnia and Physical Activity

Health-related quality of life outcomes for general health, pain, vitality, social functioning, emotional role and mental health will be measured by the Short Form 36 (SF-36, IQOLA) survey. In addition, the EORTC QLQ-C30 (cancer) and EORTC PR-25 (prostate

cancer) surveys will also be provided to measure cancer-specific indices of quality of life. Specifically, the EORTC QLQ-C30 includes five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain) a global health/quality of life scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulty); whereas the EORTC PR-25 also assesses urinary symptoms, bowel symptoms, treatment-related symptoms and sexual functioning. The FACIT Fatigue questionnaire will be administered to directly assess cancer-related fatigue. The Brief Symptom Inventory (BSI-18) will be used to assess psychological distress for anxiety, depression, somatisation and global distress severity domains. The Insomnia Severity Index (ISI) will be used to measure sleep quality disturbance, and the Godin Leisure-Time Exercise questionnaire will examine self-reported physical activity levels.

Exercise Program

Participants assigned to the exercise arm will be required to participate in a modular, multi-modal exercise intervention with spinal isometric training (M3EP-SIT) for 12 weeks (3 months). The combined M3EP-SIT program requires participants to attend three clinic-based exercise sessions each week spanning 60 minutes in duration (including warm-up and cool-down), supervised by an accredited exercise physiologist (AEP; Exercise and Sport Science Australia) and autoregulated in collaboration with the patient (i.e. adjusted based on the patients presentation at each session). Participants will also be asked to perform the SIT program during two additional home-based exercise sessions each week spanning approximately 15 minutes in duration from Week 3 onwards to allow initial familiarisation and competency assurance during the first two weeks. During the combined M3EP-SIT sessions, spinal isometric training will be provided first, followed by the modular multi-modal exercise program (Table 3).

The modular, multi-modal exercise (M3EP) component of the program will be comprised of resistance, aerobic and flexibility exercises in accordance with Galvão and colleagues[9]. This M3EP component is designed to minimise loads on affected skeletal sites through-out the body. Exercise prescriptions will be modified based on the location and extent of bone metastases for all activities (Table 4). Resistance exercise will be set using repetition maximums (RM). Participants will be asked to perform 6 different resistance exercises using major muscle groups, subject to the location and extent of bone metastases, at 8-12 RM for 3 sets per exercise to achieve moderate intensity and volume. Aerobic exercise will be set using age-predicted heart rate maximum (HRmax). Participants will undertake cardiovascular exercise using cycle ergometers, performing moderate-to-high intensity (60-85% HRmax) interval training for a total duration of 20 minutes, and monitored using heart rate monitors (Polar Electro Oy, Finland). Flexibility exercise will involve static stretching of all joints considered important for function, and for all muscles engaged during the session. All stretches will involve 2-4 sets per muscle group with a 30-60 second hold per set. All resistance and aerobic exercise prescriptions will be progressive and periodised in accordance with each patient's individually determined physical capabilities and known contraindications.

The spinal isometric training (SIT) component of the program will comprise of exercises that isometrically load deep spinal muscles. These will be performed 5 times per week. Three sessions will be supervised by an AEP synonymous with the M3EP component at an exercise clinic; with an additional two sessions self-managed by the participant. This SIT component is designed to directly target and stimulate spinal lesion site(s) through muscular contraction, thus isometric exercises have been designed to activate the full spinal column due to the commonality of lesions in thoracic and lumbar regions; the feasibility of which has been demonstrated[60]. The SIT program will require the participants to perform five exercises in whole and partial weight-supported prone and supine positions on the floor, whilst maintaining

a neutral spine (isometrically) during gentle and dynamic accessory movements. If floor exercises are contraindicated for the patient due to physical restrictions, alternate seated and standing isometric exercises are also provided. All patients will be initially provided with familiarisation of breathing technique, trunk stabilisation and hip control. Basic spinal isometric exercises will first be used to ensure safe and correct technique prior to progressing to intermediate or more challenging exercises which include less stability or dynamic accessory movements[61]. Isometric progression of patients from beginner to advanced exercises will be individually determined on the basis of their physical capabilities and known contraindications. An assortment of spinal isometric exercises canvassing the beginner to advanced, floor to standing spectrum are described in Supplementary Tables, with an assortment of sample photographs provided in the Supplementary Figure for prone and supine floor-based exercises.

Statistical Analysis

Data will be analysed using SPSS (IBM Corporation; Chicago, IL, USA). Normality of distribution for continuous variables will be determined using the Kolmogorov-Smirnov test and visual inspection of the data. Analyses will include standard descriptive characteristics, t-tests, and two-way (group x time) repeated measures ANOVA (or analysis of covariance as appropriate) to examine differences between groups over time. Any data that is not normally distributed will be log-transformed or non-parametric tests will be used. For categorical variables, the Pearson Chi-square test will be used. An alpha level of $p \leq 0.05$ will be applied to establish statistical significance. Effect sizes will also be calculated in accordance with Hopkins[62]: $d \geq 0.2$ is small; $d \geq 0.6$ is moderate; $d \geq 1.2$ is large; $d \geq 2.0$ is very large. Incomplete data and missing values will be primarily managed using an intention-to-treat approach[63] with multiple imputation; specifically using maximum likelihood imputation of missing values. To ensure the robustness of our findings, a secondary sensitivity analysis[64] will be conducted using a complete cases approach.

Dissemination

Outcomes of this trial will be broadly disseminated through various communication channels to maximise the potential for further research and development. If proven to be safe, feasible and efficacious, the outcomes will form the basis of future phase II and phase III clinical trials. To ensure a high level of delivery to clinicians, practitioners, patients and scientists, outcomes will be disseminated through national and international clinical, patient and conference presentations, as well as publication in high-impact, peer-reviewed journals. On completion of the trial and following publication of the primary manuscripts, data requests can be submitted to the study investigators at the Exercise Medicine Research Institute (Edith Cowan University, Perth, WA, Australia).

DISCUSSION

Metastatic prostate carcinoma spreads to bone in over 80% of advanced prostate cancer cases and is presently an incurable, yet treatable stage of the disease during palliation[1-8]. Consequently, these patients are provided with a suite of treatments that serve to manage pain and slow tumour progression, including ADT, radiotherapy and chemotherapy. While beneficial, these treatments produce an array of burdensome side-effects leading to considerable morbidity. The effectiveness of exercise as an adjuvant therapy to minimise, manage and in some cases reverse the adversities of primary therapies has been demonstrated[14-25]. Exercise has also shown synergistic potential with primary treatments, subsequently improving their potency; for example, enhancing chemotherapy through increased tumour vascularity to enable greater cytotoxic delivery at tumour sites[26-31]. However, the direct influence of exercise on tumour biology remains largely unknown, despite many hypothesised mechanical and non-mechanical mechanisms of action[26,65-70]. To date, orthotopic animal models have provided compelling new insight into the ability of mechanical stimulation to

interfere with tumour-driven remodelling in skeletal tissue containing human breast cancer cells[48-51]. Given that exercise is a dose-dependent mechanical stimulant which can be safely prescribed to advanced prostate cancer patients with bone metastases[9,10], it is of interest to examine whether similar modulatory interference of tumour formation and growth is achievable in humans.

This study will evaluate the feasibility, safety and preliminary efficacy of combining spinal isometric training with a modular, multimodal exercise program to provide a non-invasive, low-cost, innovative and scalable therapy in the management of advanced prostate cancer. Specifically, this study will examine the modulatory potential of direct and targeted mechanical loading of sclerotic bone lesions through isometric exercise to deliver muscle contractile forces that may suppress localised tumour formation in spinal bone metastases; mediate systemic activity of metastatic biomarkers HIF-1α (local hypoxia) and TGF-β (tumour activity); reduce bone pain; and preserve localised and surrounding musculoskeletal mass and structure. In addition, this study will also examine the multidimensional effects of exercise in advanced prostate cancer patients with bone metastases on muscle-bone health; adiposity; physical fitness; functional capacity; and psychosocial health. The outcomes of this study will provide innovative, new evidence that may be used to pursue larger phase II and phase III clinical trials to determine the efficacy of exercise on tumour suppression or regression in patients with sclerotic bone metastases secondary to prostate cancer. The outcomes of this study may also stimulate research into osteolytic or mixed bone metastases models with other primary cancer diagnoses; and may also inform the development of effective pharmaceuticals for treatment. Lastly, this study presents an exercise intervention that, if effective following larger randomised controlled trials, can inevitably be delivered in clinical and community settings by exercise physiologists.

Acknowledgements

The authors would like to thank Miss. Thea Richardson (Australian Prostate Cancer Research), Dr. Kirk Feindel (Centre for Microscopy, Characterisation and Analysis; University of Western Australia), Mr. Joey Chua (InSight Clinical Imaging), Mr. Kyle Smith (Vario Health Clinic; Edith Cowan University), Mrs. Claire Mason (Exercise Medicine Research Institute; Edith Cowan University) and Mr. Derek Atkinson (Consumer Representative) for their contributions.

Contributors

NHH, DAG, RUN and NAS developed the study concept and protocols and initiated the project. DRT, SKC, DJJ, KTF, ADR and TF assisted in further development of the protocol. NHH, DAG, RUN, DRT and SKC drafted the manuscript. NAS, DJJ, KTF, ADR and TF will provide access to patients. NHH, DAG and RUN will implement the protocol and oversee collection of data. All authors contributed and approved the final manuscript.

Funding

This project is funded by Cancer Council Western Australia (Early Career Investigator Award), and supported by Exercise Sport Science Australia (Clinical Exercise Physiology Research Grant). DAG is funded by Prostate Cancer Foundation of Australia (Movember New Directions Development Award) and Cancer Council Western Australia (Research Fellowship). SKC is supported by Australian Research Council (Professorial Future Fellowship). ADR is funded by Cancer Council Western Australia (Clinical Research Fellowship).

Competing Interests

None declared.

Ethics Approval

Human Research Ethics Committees: Edith Cowan University, and Sir Charles Gairdner and Osborne Park Health Care Group, Perth, Western Australia, Australia.

REFERENCES

1. Hall CL, Bafico A, Dai J, *et al*. Prostate cancer cells promote osteoblastic bone metastases through Wnts. *Cancer Res*. 2005;65:7554-7560.

2. Keller ET, Brown J. Prostate cancer bone metastases promote both osteolytic and osteoblastic activity. *J Cell Biochem*. 2004;91:718-729.

3. Mundy GR. Metastasis to bone: Causes, consequences and therapeutic opportunities. *Nat Rev Cancer*. 2002;2:584-593.

4. Keller ET, Zhang J, Cooper CR, *et al*. Prostate carcinoma skeletal metastases: cross-talk between tumour and bone. *Cancer and Metastasis Rev*. 2001;20:333-349.

5. Suva LJ, Washam C, Nicholas RW, *et al*. Bone metastasis: Mechanisms and therapeutic opportunities. *Nat Rev Endocrin.* 2011;7:208-218.

6. Guise TA, Mohammad KS, Clines G, *et al*. Basic mechanisms responsible for osteolytic and osteoblastic bone metastases. *Clin Cancer Res*. 2006;12:6213-6216.

7. Lee RJ, Saylor PJ, Smith MR. Treatment and prevention of bone complications from prostate cancer. *Bone*. 2011;48:88-95.

8. Logothetis CJ, Lin SH. Osteoblasts in prostate cancer metastasis to bone. *Nat Rev Cancer*. 2005;5:21-28.

9. 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;11:517-523.

10. Cormie P, Newton RU, Spry N, *et al*. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate Cancer Prostatic Dis*. 2013;16:328-335.

11. Coleman RE. Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity. *Clin Cancer Res*. 2006;12:6243-6249.

12. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*. 2000;88:2989-2994.

13. Saad F, Olsson C, Schulman CC. Skeletal morbidity in men with prostate cancer: Quality-of-life considerations throughout the continuum of care. *Eur Urol.* 2004;46:731-739.

14. Kenfield SA, Stampfer MJ, Giovannucci E, *et al*. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol*. 2011;29:726-732.

15. Galvão DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol*. 2005;23:899-909.

16. Newton RU, Galvão DA. Exercise in prevention and management of cancer. *Curr Treat Options Oncol*. 2008;9:135-146.

17. Singh F, Newton RU, Galvão DA, *et al*. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol*. 2013;22:91-104.

18. 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;14:485-493.

19. Buffart LM, Galvão DA, Chinapaw MJ, *et al*. Mediators of the resistance and aerobic exercise intervention effect on physical and general health in men undergoing androgen deprivation therapy for prostate cancer. *Cancer*. 2014;120:294-301.

20. Newton RU, Galvão DA. Exercise medicine for prostate cancer. *Eur Rev Aging Phys Act*. 2013;10:41-45.

21. Cormie P, Galvão DA, Spry N, *et al*. 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*. 2014;22:1537-1548.

22. Hayes SC, Spence RR, Galvão DA, *et al*. Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. *J Sci Med Sport*. 2009;12:428-434.

23. Buffart LM, Galvão DA, Brug J, *et al*. Evidence-based physical activity guidelines for cancer survivors: Current guidelines, knowledge gaps and future research directions. *Cancer Treat Rev*. 2014;40:327-340.

24. Galvão DA, Taaffe DR, Spry N, *et al*. 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(2):340-347.

25. Galvão DA, Spry N, Taaffe DR, *et al*. Exercise can prevent and even reverse adverse effects of androgen suppression treatment in men with prostate cancer. *Prostate Cancer Prostatic Dis*. 2007;10:340-346.

26. Betof AS, Lascola CD, Weitzel DH, *et al*. Modulation of murine breast tumour vascularity, hypoxia and chemotherapeutic response by exercise. *J Natl Cancer Inst*. 2015;107:1-6.

27. Hoffman P. Exercise training, tumour metabolism, tumour-host interaction and lactate shuttle theory. *Front Pharmacol*. 2014.

28. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: A translational perspective. *Brain Behav Immun*. 2013;30:S75–S87.

29. Jones LW, Dewhirst MW. Therapeutic properties of aerobic training after a cancer diagnosis: More than a One-Trick Pony? *J Natl Cancer Inst*. 2014;106:1-3.

30. 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*. 2012;113:263-272.

31. Jones LW, Fels DR, West M, *et al*. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prev Res*. 2013;6:925-937.

32. Wolff G, Balke JE, Andras IE, *et al*. Exercise modulates redox-sensitive small GTPase activity in the brain microvasculature in a model of brain metastasis formation. *PLoS One*. 2014;9:1-8.

33. Glass OK, Inman BA, Broadwater G, *et al*. Effect of aerobic training on the host systemic milieu in patients with solid tumours: An exploratory correlative study. *Br J Cancer*. 2015;112:825-831.

34. Galvão DA, Nosaka K, Taaffe DR, *et al*. Endocrine and immune responses to resistance training in prostate cancer patients. *Prostate Cancer Prostatic Dis*. 2008;11:160-165.

35. Galvão DA, Spry N, Denham J, *et al*. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol*. 2014;65:856-864.

36. Galvão DA, Spry N, Taaffe DR, *et al*. A randomized controlled trial of an exercise intervention targeting cardiovascular and metabolic risk factors for prostate cancer patients from the RADAR trial. *BMC Cancer*. 2009;9:419-426.

37. Galvão DA, Newton RU, Taaffe DR, *et al*. Can exercise ameliorate the increased risk of cardiovascular disease and diabetes associated with ADT? *Nat Clin Pract Urol*. 2008;5:306-307.

38. Beydoun N, Bucci JA, Chin YS, *et al*. Prospective study of exercise intervention in prostate cancer patients on androgen deprivation therapy. *J Med Imaging Radiat Oncol*. 2014;58:369-376.

39. Newton RU, Taaffe DR, Spry N, *et al*. Can exercise ameliorate treatment toxicity during the initial phase of testosterone deprivation in prostate cancer patients? Is this more effective than delayed rehabilitation? *BMC Cancer*. 2012;12:432-440.

40. Galvão DA, Taaffe DR, Spry N, *et al*. Acute versus chronic exposure to androgen suppression for prostate cancer: Impact on the exercise response. *J Urol*. 2011;186:1291-1297.

41. Cormie P, Galvão DA, Spry N, *et al*. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: A randomized controlled trial. *BJU Int*. 2014;115:256-266.

42. Garland SN, Johnson B, Palmer C, *et al*. Physical activity and telomere length in early stage breast cancer survivors. *Breast Cancer Res*. 2014;16:413-422.

43. Shammas MA. Telomeres, lifestyle, cancer, and aging. *Curr Opin Clin Nutr Metab Care*. 2011;14:28–34.

44. Ludlow AT, Zimmerman JB, Witkowski S, *et al*. Relationship between Physical Activity Level, Telomere Length, and Telomerase Activity. *Med Sci Sports Exerc*. 2008;40:1764–1771.

45. Heber S, Volf I. Effects of physical (in)activity on platelet function. *Biomed Res Int*. 2015;14:1-11.

46. Sharma D, Brummel-Ziedins KE, Bouchard BA, *et al*. Platelets in tumor progression: A host factor that offers multiple potential targets in the treatment of cancer. *J Cell Physiol*. 2014;229:1005-1015.

47. Egan K, Cooke N, Kenny D. Living in shear: Platelets protect cancer cells from shear induced damage. *Clin Exp Metastasis*. 2014;31:697-704.

48. Wang J, Lu D, Mao D, *et al*. Mechanomics: An emerging field between biology and biomechanics. *Protein Cell*. 2014;5:518-531.

49. Lynch ME, Fischbach C. Biomechanical forces in the skeleton and their relevance to bone metastasis: Biology and engineering considerations. *Adv Drug Deliv Rev*. 2014;79-80:119-134.

50. 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.

51. Chen X, Goh JCH, Teoh SH, *et al*. Localized sclerotic bone response demonstrated reduced nanomechanical creep properties. *J Mech Behav Biomed Mater*. 2013;17:198-208

52. Lecouvet FE, Talbot JN, Messiou C, *et al*. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer*. 2014;50:2519-2531.

53. Shah LM, Salzman KL. Imaging of Spinal Metastatic Disease. *Int J Surg Oncol*. 2011;2011:769753

54. Tombal B, Lecouvet F. Modern detection of Prostate Cancer's Bone Metastasis: Is the bone scan era over? *Adv Urol*. 2012;2012:893193

55. Yushkevich PA, Piven J, Hazlett HC, *et al*. User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage*. 2006;31(3):1116-28.

56. Dunn LK, Mohammad KS, Fournier PG, *et al*. Hypoxia and TGF-β Drive Breast Cancer Bone Metastases through Parallel Signaling Pathways in Tumor Cells and the Bone Microenvironment. *PLoS One*. 2009;4:e6896.

57. Hart NH, Nimphius S, Spiteri T, *et al*. Segmental musculoskeletal examinations using dual-energy X-ray absorptiometry (DXA): Positioning and analysis considerations. *J Sport Sci Med*. 2015;14:620-626

58. Hologic. QDR for Windows XP Reference Manual. *Hologic Inc*. 2014

59. Hart NH, Nimphius S, Weber J, *et al*. Musculoskeletal asymmetry in football athletes: A product of limb function over time. *Med Ex Sport Sci*. 2016;15:1379-1387.

60. 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;14:67-77.

61. McGill SM. Low back stability: from formal description to issues for performance and rehabilitation. *Exer Sport Sci Rev*. 2001;29:26–31.

62. Hopkins WG. A scale of magnitudes for effect statistics. *SportScience*. 2002. http://www.sportsci.org/resource/stats/effectmag.html. Accessed 15 Jan 2016.

63. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res*. 2011;2:109-112.

64. Thabane L, Mbuagbaw L, Zhang S, *et al*. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol*. 2013;13:92.

65. Jones LW, Alfano CM. Exercise-oncology research: Past, present, and future. *Acta Oncol*. 2013;52:195-215

66. Pedersen L, Christensen JF, Hojman P. Effects of Exercise on Tumor Physiology and Metabolism. *Cancer J*. 2015;21:111-116

67. Secomb TW, Alberding JP, Hsu R, *et al*. Angiogenesis: An adaptive dynamic biological patterning problem. *PLoS Comput Biol*. 2013;9:e1002983.

68. Siemann DW, Horsman MR. Modulation of the tumor vasculature and oxygenation to improve therapy. *Pharmacol Ther*. 2015;153:107-124.

69. Ergun M, Eyigor S, Karaca B, *et al*. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *Eur J Cancer Care*. 2013;22:626–637

70. Galvão DA, Taaffe DR, Spry N, *et al*. Enhancing Active Surveillance for Men with Prostate Cancer: The Potential Role of Exercise Medicine. *Nat Rev Urol*. 2016:13:258-265.

LEGEND OF FIGURES

Figure 1. Schematic overview of the study protocol. MRI = Magnetic Resonance Imaging; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; 1RM = One Repetition Maximum.

Figure 2. Example MRI image acquisition. [Left]: cervical, thoracic and lumbar scout views stitched together with two sclerotic lesions identified at T8 and T11. [Top, Middle]: thoracic scout view at higher resolution with the T11 vertebrae magnified. [Bottom, Middle]: example data outputs provided by regional analysis. [Right] slice by slice, cephalad to caudal, transverse view at each level of the T11 lesion, with an example colour map and tumoural analysis of one slice in isolation.

LEGEND OF TABLES

Table 1. Schedule of assessments at baseline, on-trial and post-intervention

Table 2. Assessments of study feasibility

Table 3. Weekly distribution of testing, M3EP and SIT exercise sessions across the exercise intervention

Table 4. Modular multi-modal exercise program (M3EP) for patients with bone metastases [9,10]

LEGEND OF SUPPLEMENTARY FILES

Supplementary File 1. Floor-based, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for varying physical capabilities and training progression rates.

Supplementary File 2. Seated and standing, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for patients unable to perform floor-based exercises.

Supplementary File 3. Photographic examples of prone (left) and supine (right) floor-based spinal isometric exercises, illustrating the start position and final hold positions of each labelled exercise to assist exercise physiologists and cancer patients.

Table 1. Schedule of assessments at baseline and post-intervention.

Measures	Baseline	Post-Intervention
Tumour Morphology – (off-site)		
- MRI Scan: T1-Axial	X	X
Tumour Biomarkers		
- Blood: HIF-1α, TGF-β	X	X
Anthropometry		
- Height (cm)	X	
- Weight (kg)	X	X
- Waist Circumference (cm)	X	X
- Hip Circumference (cm)	X	X
- Femoral Length (mm)	X	
- Tibial Length (mm)	X	
- Body Mass Index (kg/m^2)	X	X
- Waist-to-hip ratio	X	X
Body Composition		
- DXA Scans: Whole-body, Spinal, Hip	X	X
- pQCT Scans: Femoral, Tibial	X	X
Physical Assessments		
- NeuroCom Balance Test	X	X
- 1RM Strength Test (Leg Extension)	X	X
- 400m Walk Test	X	X
- Timed Up and Go Test	X	X
Other Biomarkers – (off-site)		
- Blood: P1NP, ALP, CRP, Fasting Glucose and Lipids, PSA	X	X
- Urine: NTx	X	X
Questionnaires		
- Demographic and Health History	X	
- Concomitant Medications	X	X
- Health-related Quality of Life (SF-36)	X	X
- Cancer-specific Quality of Life (EORTC: QLQ30, PR25)	X	X
- Brief Symptom Index (BSI-18)	X	X
- Insomnia Severity Index (ISI)	X	X
- Godin Leisure-time Exercise	X	X
Exercise Program		
- Clinic Exercise Record Sheet (Prescribed vs. Actual)	At each exercise session	
- Home Exercise Record Sheet (Prescribed vs. Actual)	At each exercise session	

Note: HIF-1α = Hypoxia-Inducible Factor 1-alpha; TGF-β = Transformation Growth-like Factor beta; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; P1NP = amino-terminal propeptide of type 1 procollagen; NTx = amino-terminal collagen type-1 telopeptide; ALP = Alkaline Phosphate; CRP = C-Reactive Protein; PSA = Prostate-Specific Antigen; SF-36 = Short Form-36; EORTC = European Organisation for Research and Treatment of Cancer.

Table 2. Assessments of study feasibility.

Measures	Time of Collection
Recruitment and Completion	
- Referred Patients	Trial Completion
- Eligible Patients	Trial Completion
- Enrolled Patients	Trial Completion
- Eligibility Rate	Trial Completion
- Recruitment Rate	Trial Completion
- Trial Completions	Trial Completion
- Patient Withdrawals	Trial Completion
- Patient Drop-Outs	Trial Completion
- Trial Contamination	Trial Completion
Patient Safety – (Control Arm)	
- Number of Adverse Events	Tri-weekly Record
- Severity of Adverse Events	Tri-weekly Record
- Number of Skeletal Complications	Tri-weekly Record
Patient Safety – (Intervention Arm)	
- Number of Adverse Events	At each exercise session
- Severity of Adverse Events	At each exercise session
- Number of Skeletal Complications	At each exercise session
Program Tolerance – (Intervention Arm)	
- Pre-Sessional Bone Pain	At each exercise session
- Pre-Sessional Fatigue	At each exercise session
- Sessional Rating of Perceived Exertion	At each exercise session
- Sessional Tolerance	At each exercise session
Program Adherence– (Intervention Arm)	
- Number of Completed Sessions	Post-Intervention
- Number of Missed Sessions	Post-Intervention
Program Compliance – (Intervention Arm)	
- Prescribed vs. Actual Exercise completed – [*for each exercise mode*].	Post-Intervention
- Percent of Total Volume completed – [*for each exercise mode*].	Post-Intervention

Table 3. Weekly distribution of testing, M3EP and SIT exercise sessions across the exercise intervention.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 0	Baseline Testing						
Week 1 to Week 2	SIT M3EP	---	SIT M3EP	---	SIT M3EP	REST	REST
Week 3 to Week 12	SIT M3EP	SIT	SIT M3EP	SIT	SIT M3EP	REST	REST
Week 13	Post-Intervention Testing						

Note: SIT = Spinal Isometric Training (15 minutes); M3EP = Modular Multi-Modal Exercise Program (60 minutes). Clinic exercise sessions occur on Monday, Wednesday and Friday; home isometric exercise sessions occur on Tuesday and Thursday. Spinal isometric exercises are provided at the start of all clinic exercise sessions (following a general warm-up). Home-based SIT start from Week 3 onwards to enable appropriate familiarisation and training during the first two weeks of the program.

Table 4. Modular multi-modal exercise program (M3EP) for patients with bone metastases [9,10]

	Resistance			Aerobic		Flexibility
Metastases Site	**Upper**	**Trunk**	**Lower**	**WB**	**NWB**	**Static**
Pelvis	√	√	√**		√	√
Lumbar Spine	√		√		√	√***
Thoracic Spine / Ribs	√*		√	√	√	√***
Proximal Femur	√	√	√**		√	√
All Regions	√*		√**		√	√***

Note: √ = 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.

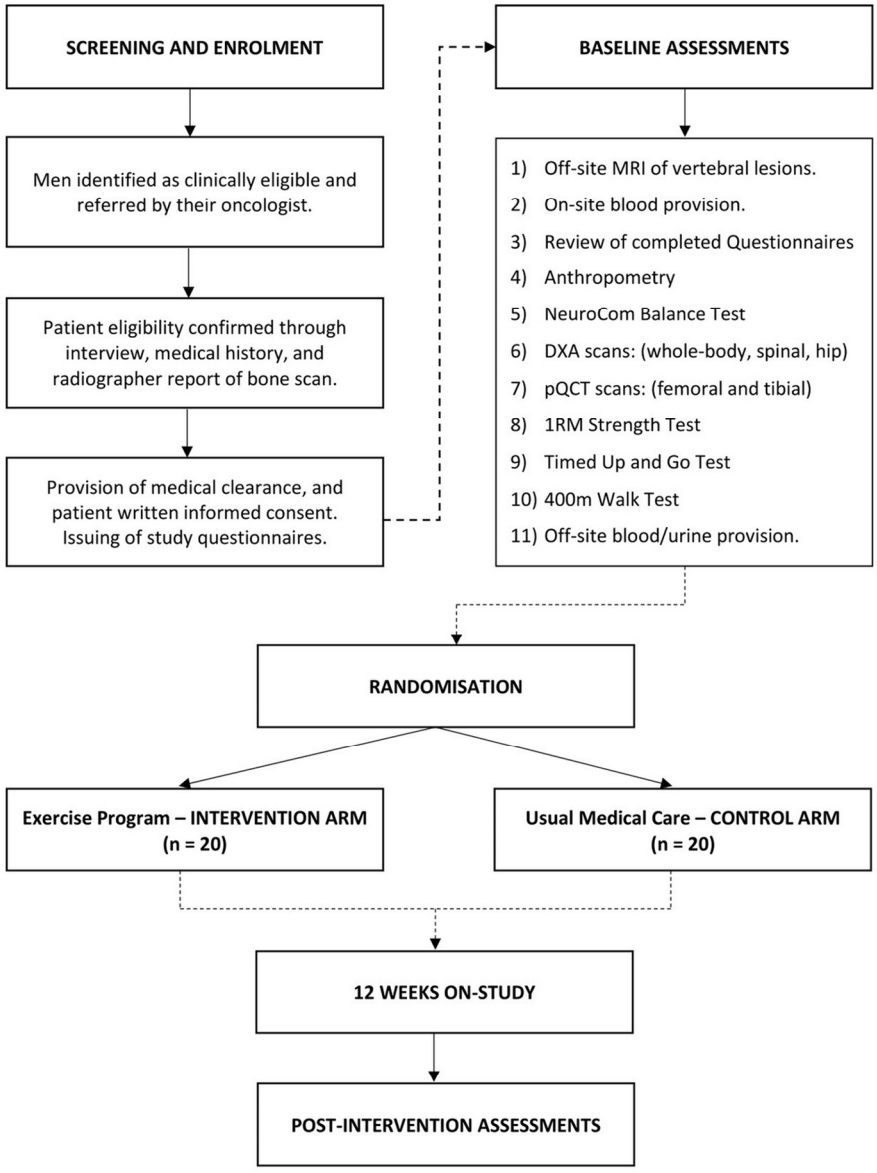


Figure 1. Schematic overview of the study protocol. MRI = Magnetic Resonance Imaging; DXA = Dual-energy X-ray Absorptiometry; pQCT = peripheral Quantitative Computed Tomography; 1RM = One Repetition Maximum.
Figure 1
107x139mm (300 x 300 DPI)

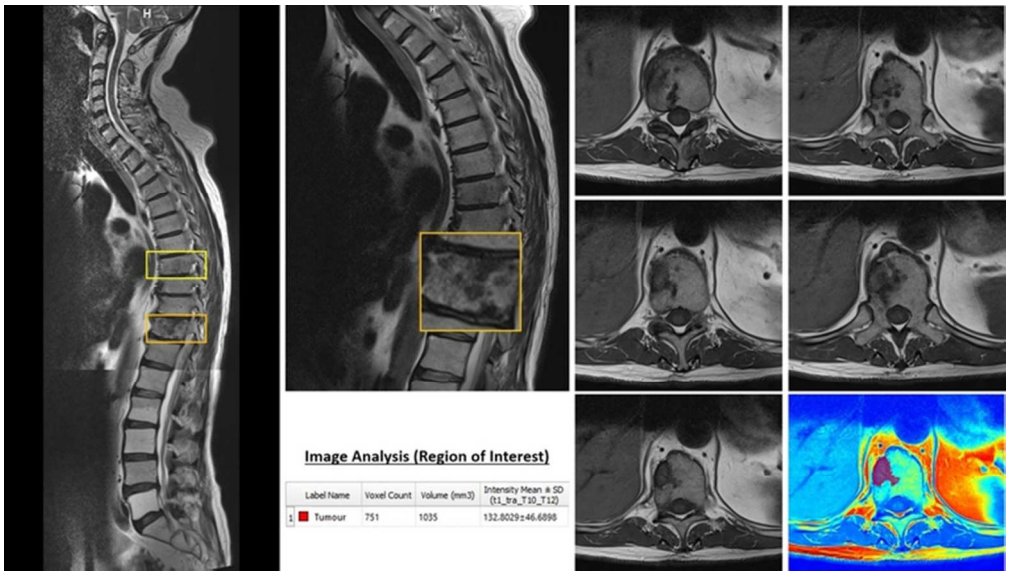


Figure 2. Example MRI image acquisition. [Left]: cervical, thoracic and lumbar scout views stitched together with two sclerotic lesions identified at T8 and T11. [Top, Middle]: thoracic scout view at higher resolution with the T11 vertebrae magnified. [Bottom, Middle]: example data outputs provided by regional analysis. [Right] slice by slice, cephalad to caudal, transverse view at each level of the T11 lesion, with an example colour map and tumoural analysis of one slice in isolation.
Figure 2
64x36mm (300 x 300 DPI)

Supplementary Table 1. Floor-based, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for varying physical capabilities and training progression rates.

Exercise	Instruction
Abdominal Brace #1: - Single Leg Lift	**Start position:** Supine on floor with arms by their side, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise one foot off the floor until shank is parallel to the floor. Hold for 10 seconds. Lower foot to floor and repeat on the other limb. **Volume:** Perform 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Abdominal Brace #2: - Double Leg Lift	**Start position:** Supine on floor with arms by their side, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise both feet off the floor until both shanks are parallel to the floor. Hold for 10 seconds. Lower both feet to floor. **Volume:** Perform 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Abdominal Brace #3: - Leg Fall Out	**Start position:** Supine on floor with hands resting on hips, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly allow one leg to rotate outward towards the floor by relaxing the adductor muscles. Do not allow rotation at the spine or pelvis. Repeat on opposite leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
Abdominal Brace #4: - Foot Slide	**Start position:** Supine on floor with hands resting on hips, knees bent and feet on the floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly slide one leg out (extending at the hip and knee) and back along the floor. Repeat on opposite leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
'All Fours' Position #1: - Hip Hinges	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly flex at the hips and knees, moving backward. Patient should sit into this position so that their buttocks touches their heels while arms remain fixed. Return to start position. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 15 seconds between sets.
'All Fours' Position #2: - Arm Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one arm off the ground. Maintain balance by holding a neutral and firm spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on alternate arm. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
'All Fours' Position #3: - Leg Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one leg off the ground. Maintain balance by holding a neutral and firm spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on alternate leg. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
'All Fours' Position #4: - Arm & Leg Extension	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one arm and the opposite leg off the ground. Maintain balance by holding a neutral spine. Pause for 5 seconds before slowly lowering back to the floor. Repeat on the alternate arm/leg combination. **Volume:** 2-4 sets of 8-12 repetitions. **Rest:** 30 seconds between sets.
Bridge #1: - Full Hip Extension	**Start position:** Supine on floor with hands by their side, knees bent and feet on the floor. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Pause for 5 seconds in this position prior to slowly lowering hips back to the floor. **Volume:** 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.

Bridge #2: - Single Hip Extension	**Start position:** Supine on floor with hands by their side, knees bent and feet on the floor. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Once in this position, slowly extend and straighten one leg. Slowly return extended leg back to the floor before also lowering the hips back to the floor. Alternate between legs. **Volume:** 2-4 sets of 8-12 repetitions. **Rest:** 60 seconds between sets.
Bridge #3: - Side Bridges	**Start position:** Lying on their side, with arm abducted, resting on their forearm. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift hips to align with shoulders and knees. Maintain knee contact with the floor. Hold this position for up to 90 seconds (or as long as achievable without compromising technique). Alternate sides. This can be progressed by performing this exercise with legs fully extended (resting on forearm and feet). **Volume:** Hold for 10- 90 seconds. Repeat 2-4 times. **Rest:** 60 seconds between sets.
Bridge #4: - Prone Planks	**Start position:** Prone, resting on knees, with outstretched hands beneath the shoulders. **Instructions:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Straighten legs while arms remain outstretched, ensuring abdominals remain braced. Hold this position for up to 90 seconds (or as long as achievable without compromising technique). This can be progressed by performing this exercise while resting on forearms. **Volume:** Hold for 10-90 seconds. Repeat 2-4 times. **Rest:** 60 seconds between sets.

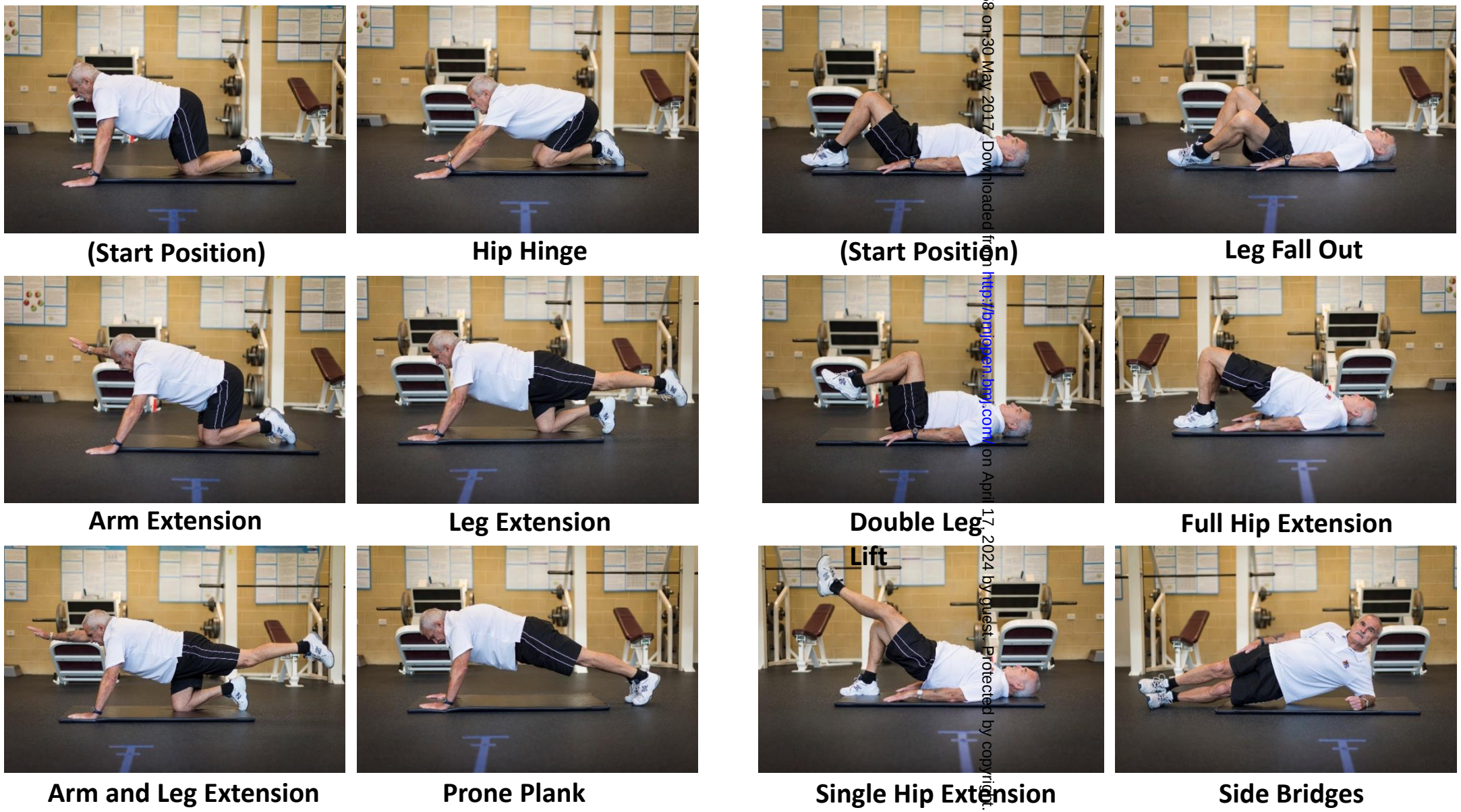
Note: Always maintain neutral spine and control pelvic tilt. Spine must be supported through abdominal bracing to ensure safe delivery of these exercises [60]. Practitioners must always be cautious and observant to ensure correct technique and posture is upheld. Patients with cervical bone metastases are contraindicated for Bridge #1 or Bridge #2 and should not perform these two exercises.

Supplementary Table 2. Seated and standing, spinal isometric exercise library for prostate cancer patients with spinal bone metastases to cater for patients unable to perform floor-based exercises.

Exercise	Instruction
Seated Exercise #1 - Marching	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Lift one knee up as high as flexibility allows (while maintaining upright posture). Pause at the top for 2 seconds and lower back down. Repeat with the opposite limb. Only one foot should be on the ground at a time to simulate slow paced marching. Focus on patient posture and trunk stability to ensure proper muscle activation. To increase difficulty, **Volume:** Perform 2-4 sets of 8-12 repetitions (each leg). **Rest:** 30 seconds between sets.
Seated Exercise #2 - Leg Extension	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly raise one foot off the floor to straighten the leg (until the shank is parallel to the floor). Hold for 5 seconds. Lower the foot to the floor. Repeat on the other leg. To increase difficulty, if seated on a stable bench (or chair), patient can use both legs simultaneously. Alternatively, patients can perform single-leg extensions against theraband resistance or while seated on a fit-ball. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** Perform 2-4 sets of 8-12 repetitions (each leg). **Rest:** 30 seconds between sets.
Seated Exercise #3 - Theraband Row	**Start position:** Seated on bench or fit-ball; back straight, knees bent and feet on floor. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Wrap an elastic band around a fixed object at chest level in front of the patient. Use a band which provides a mild resistance. With arms fully extended, slowly pull the band towards the chest, keeping the elbows low and close to the body, until the elbows bend to approximately 90 degrees. Hold position for 5 seconds. Slowly return to the start position. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
Hybrid Exercise #1 - Sit-to-Stand	**Start position:** Seated on a bench or chair; back straight with arms crossed over. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Stand up from the seated position. Once fully upright, return slowly to a seated position. Aim is to perform this exercise without using arms for assistance (if possible). Avoid this exercise if patient has knee pathology. Focus on patient posture and **movement quality** to ensure proper muscle activation and safe performance of this exercise. **Volume:** 2-4 sets of 8 repetitions **Rest:** 60 seconds between sets.
Standing Exercise #1 - Wall Push-Up	**Start position:** Standing. Place hands on wall at shoulder height, with arms extended. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Slowly lower their body and hips towards the wall by bending at the elbows in a controlled manner. Once their face is near the wall, hold for 5 seconds and then slowly push against the wall to extend the arms and return back to starting position. Focus on patient posture and trunk stability to ensure proper muscle activation. To increase difficulty, patient can increase angle against the wall. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.
Standing Exercise #2 - Wall Plank	**Start position:** Standing. Leaning forward on forearms against a wall. **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). While leaning on forearms against the wall, slowly move feet backward to desired angle between the body and wall. Focus on placing body weight onto forearms while keeping trunk muscle engaged, torso straight with neutral spine. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.

Standing Exercise #3 - Theraband Row	**Start position:** Standing; back straight, split-stance (one foot forward, one foot back). **Instruction:** Pre-activate and set abdominals to hold a neutral spine position (isometric). Wrap an elastic band around a fixed object at chest level in front of the patient. Use a band which provides a mild resistance. With arms fully extended, slowly pull the band towards the chest, keeping the elbows low and close to the body, until the elbows bend to approximately 90 degrees. Hold position for 5 seconds. Slowly return to the start position. Focus on patient posture and trunk stability to ensure proper muscle activation. **Volume:** 2-4 sets of 8-12 repetitions **Rest:** 30 seconds between sets.

Note: Always maintain an upright trunk (straight back) with neutral spine and control pelvic position during all exercises. Spine must be supported through abdominal bracing to ensure safe delivery of these exercises [60]. Practitioners must always be cautious and observant to ensure correct technique and posture is upheld.



Supplementary Figure 3. Photographic examples of prone (left) and supine (right) floor-based isometric exercises, illustrating the start position and final hold positions of each labelled exercise to assist exercise physiologists and cancer patients. The patient in-set was approached in order to obtain these photos explicitly for this manuscript, and has signed a media release consent form.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – Page 3
	2b	All items from the World Health Organization Trial Registration Data Set – N/A
Protocol version	3	Date and version identifier – N/A
Funding	4	Sources and types of financial, material, and other support – Pg. 19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – Pg. 19
	5b	Name and contact information for the trial sponsor – Pg. 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – N/A
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – Pg. 4 to 6
	6b	Explanation for choice of comparators – Pg. 4 to 6.
Objectives	7	Specific objectives or hypotheses – Pg. 6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – Pg. 6 to 7

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – Pg. 6 to 7; Page 14
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – Pg. 8 to 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Pg. 6 to 7; 14 to 15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) – N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – Pg. 7, Table 2.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – Pg. 7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – Pg. 9 to 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – Figure 1, Table 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – Pg. 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – Pg. 7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – Pg. 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned, – Pg. 8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions, – Pg. 8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – Pg. 6 to 8.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – Pg. 9 to 16, Table 1, Table 2.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – Figure 1, Pg. 7.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – Pg. 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – Pg. 16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – Pg. 16

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed. – N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial – N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct – Table 2, Pg. 9 to 10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – N/A

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – Approved already – Pg. 9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – Pg. 7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – Pg. 15 to 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – Pg. 19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – Pg. 9 and Pg. 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – N/A

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – Pg. 15 to 16
	31b	Authorship eligibility guidelines and any intended use of professional writers – N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – Pg. 11

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.