GAP4 Clinical Study Protocol

INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A Multicentre, Randomised, Controlled, Phase III Study

Protocol Number:	
Investigational Product:	High intensity aerobic and resistance training
Funder:	Movember

Status: Final Protocol
Date: 19 April 2018
Prepared by: GAP4 Management Team
Approved by: GAP4 Steering Committee
Document No.: v4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AGREEMENT

I confirm that I have read this protocol. I will comply with the protocol and the principles of Good Clinical Practice (GCP), as described in the United States Code of Federal Regulation (CFR) 21 Parts 11, 50, 54, 56, and 312 and the appropriate International Conference on Harmonisation guidance documents.

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Investigator Signature *Date*

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Print Name and Title

Site Name _____

PROTOCOL SYNOPSIS

Title	**Intense exercise for survival among men with metastatic castrate-resistant prostate cancer (INTERVAL – MCRPC):** A Multicentre, Randomised, Controlled Phase III Study
Funder	Movember
Phase	III
Study Design	Randomised Controlled Trial
Primary Objective	To determine if high intensity aerobic and resistance training (Supervised Exercise) plus psychosocial support increases overall survival compared to psychosocial support alone (Self-directed Exercise) in patients with metastatic castrate-resistant prostate cancer.
Secondary Objectives	• To compare progression free survival between the Supervised Exercise (intervention) and Self-directed Exercise (control) groups. • To compare time to first occurrence of a symptomatic skeletal-related event between the intervention and control groups. • To compare time to progression of pain, degree of pain, and opiate use between the intervention and control groups. • To compare change in biomarkers of inflammation, energy metabolism, and androgen metabolism over time between the intervention and control groups. • To determine whether biomarkers of inflammation, energy metabolism, and androgen metabolism are associated with overall survival among men with mCRPC, and explore the extent to which these biomarkers mediate the hypothesized association between high-intensity aerobic and resistance exercise and survival. • To compare physical and emotional quality of life between the intervention and control groups.
Number of Patients	866

Enrolment Criteria	▪ Patients must be mCRPC. This is defined as adenocarcinoma of the prostate with systemic metastatic disease despite castrate levels of testosterone (<50 ng/dL) due to orchiectomy or LHRH agonist. o Patients must have one or more of the following to be considered mCRPC ▪ Metastatic Disease Progression: >20% increase in the sum of diameters of measurable lesions from the time of maximal regression or appearance of one or more new lesions. ▪ Bone Scan Progression: Appearance of one or more new lesions on bone scan attributable to prostate cancer. ▪ PSA Progression: PSA ≥2 ng/ml that has risen serially on at least two occasions, each at least one week apart (PSA1 < PSA2 < PSA3). ▪ Castrate levels of testosterone must be maintained while on study. Be on androgen deprivation therapy (ADT) with a GnRH agonist/antagonist or prior bilateral orchiectomy. All patients will be required to be on ADT during the study period or have had a prior bilateral orchiectomy. Men with small cell neuroendocrine tumours or features of small cell disease are not eligible. ▪ At enrolment, patients must fit into one of the following 5 categories: 1. Treatment naïve for mCRPC (have not yet started approved therapies for CRPC ie: Abiraterone/Enzalutamide/ Apalutamide/Docetaxel; less than 4 weeks on approved therapies is still considered to be treatment naïve) Or 2. Receiving Abi/Enza/Apa for mCRPC AND responding or stable (PSA values must be stable or declining after at least 4 weeks since starting Abi/Enza/Apa for mCRPC) Or 3. Patients with PSA progression while on Abi/Enza/Apa are eligible as long as they are asymptomatic AND there is no intent on starting chemotherapy within 6 months Or 4. Patients treated with Docetaxel as first line therapy for mCRPC who are asymptomatic without ANY evidence of progression Or 5. Patients may have progressed following Docetaxel first line and are now receiving treatment with Abi/Enza/Apa. These patients must absolutely be responding or stable (PSA values must be stable or declining after starting Abi/Enza/Apa treatment) and have an expected life expectancy of more than 1 year. ▪ ≥4 weeks since last major surgery and fully recovered. ▪ No known contraindications to high intensity exercise, including, but not limited to: brain metastases; current congestive heart failure (New York Heart Association Class II, III or IV); serious or non-healing wound, ulcer, or bone fracture; spinal cord compromise or instrumentation due to metastatic disease; peripheral neuropathy

	≥grade 3. No serious cardiovascular events within 12 months including, but not limited to, transient ischemic attack (TIA), cerebrovascular accident (CVA), or myocardial infarction (MI). Patients with a history of hypertension must be well-controlled (< 160/90) on anti-hypertensive therapy. ▪ Halabi Nomogram score <195[1] (Risk Category rated as low or intermediate risk) ▪ Age ≥18 years ▪ Required Baseline Laboratory Values: ANC ≥ 1500/uL; Platelet count ≥ 100,000/uL; Creatinine ≤ 1.5 x upper limits of normal; Bilirubin ≤ 1.5 x upper limits of normal; AST ≤ 1.5 x upper limits of normal; Serum testosterone ≤ 50 ng/dL ▪ ECOG performance status 0-1 ▪ Medical clearance by treating physician to undergo a symptom-limited cardiopulmonary exercise test and vigorous aerobic and resistance exercise training, and able to complete an acceptable cardiopulmonary exercise test. ▪ Exercise Coordination Centre (ECC) review and approval of subject's screening bone scan / areas with bone metastases. ▪ Men participating in vigorous aerobic exercise for >60 min/week or structured resistance exercise ≥2 days/week, are not eligible. ▪ Subject is willing and able to use technological aspects of the trial. ▪ The subject is fluent in the language as designated by the institution at which he would be enrolled.
Safety Assessments	Symptom-limited cardiopulmonary exercise test with ECG during the screening period. Physician clearance* to continue obtained every 6 cycles (1 cycle=28 days), vital signs every 6 cycles, ECOG performance status every 3 cycles, concomitant medications each cycle, and AEs assessed each cycle and reported continuously from informed consent until 28 days after cycle 24. *For any patient under that management of a cardiologist, additional clearance by his cardiologist is necessary at Cycles 0, 6, and 12.
Data Monitoring Committee	A central Data Monitoring Committee will be established to oversee the safety of all subjects enrolled in this study. The committee will receive notification every 3 months of the interim and total accrual and significant adverse events. On the discretion of the chair of the DMC, interim analyses may be scheduled as modifications to the protocol. Additional meetings during the study period may occur at the discretion of the Steering Committee. This committee will pass all recommendations to the Research Advisory Committee, who will make the final decisions about study closure, expanding eligibility criteria, etc.
Efficacy Assessments	Overall survival status and cause of death will be ascertained via review of medical and death records.
Primary Endpoint	Overall survival
Secondary Endpoints	Progression-free survival, symptomatic skeletal-related events, pain, opiate use, cancer-related fatigue, metabolic biomarkers, physical function, quality-of-life (QOL) and QOL-adjusted survival

Other Evaluations	Brief Pain Inventory Short Form (BPI-SF), World Health Organization (WHO) analgesic scale, Functional Assessment of Cancer Therapy-Prostate (FACT-G), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue Subscale), EuroQOL five dimension questionnaire (EQ-5D-5L), Godin Leisure Time Physical Activity Questionnaire, country-specific food frequency questionnaire, Pittsburgh Sleep Quality Index (PSQI); falls; memory; exercise motivation; health economics
Rationale for Number of Patients	This is a 1:1 randomised controlled trial in men with metastatic castrate-resistant prostate cancer (MCRPC). Eligible, consented participants will be randomised with equal probability to one of two intervention regimens: supervised exercise (SE) group for 48 weeks (12 x 28-day cycles) which tapers progressively to self-management with psychosocial support or psychosocial support for men in the self-directed exercise (SDE) group. Men will be stratified by treatment status at the time of randomization and site. Considering a total enrolment period of 60 months and minimum 36 months follow-up for each patient after enrolment; assuming survival time follows an exponential distribution; and assuming a median OS survival of 33.5 months in the control arm, the sample size required to detect a hazard ratio (HR) of 0.78 with 80% power at significance level of 0.05 is 824 translating to 412 men in each arm. Accounting for 5% of patients with unknown survival status at 3 years, we aim to enrol 866 men. With 80% power, we will observe median survival times (>216 events in both arms) at 66 months (5.5 years) after the first enrolment.
Statistical Analysis Plan for Primary Endpoint	An intent-to-treat approach will be used to analyse OS. Patients without death at the end of follow-up will be censored on the date of the last contact (or, if no contact after baseline, at the date of randomisation + 1 day). Kaplan-Meier methods will be used to estimate the median OS for each treatment arm as well as the 1-year, 2-year, and 3-year OS rates and corresponding 95% confidence intervals. A two-sided log-rank test stratified by treatment status at the time of registration (Y/N) and study site will be used to assess the effect of the intervention. Un-stratified log-rank tests will be examined as sensitivity analyses. Cox proportional-hazard regression models will be used to estimate the hazard ratio and its 95% confidence interval to quantify the effect of the intervention on OS, adjusting for stratification factors and other potential confounding factors.
Duration of Patient Participation and Duration of Study	All patients will be followed for OS a minimum of 36 months (for those men enrolled last during the 3 year enrolment period) after randomisation to observe median survival time in both groups. After the intervention period, participants will complete a set of surveys on a yearly basis; we will contact them, then next of kin and alternate contact, if needed, if we do not hear from them.

LIST OF ABBREVIATIONS

ADT	androgen deprivation therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
BICR	blinded independent central review
BMI	body mass index
BPI-SF	Brief-Pain Inventory Short Form
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CNS	central nervous system
CPET	cardiopulmonary exercise test
CR	complete response
CRF	case report form
CRP	c-reactive protein
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
ECC	Exercise Coordinating Centre
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FACIT	Functional Assessment of Chronic Illness Therapy
FFPE	formalin-fixed paraffin-embedded
FFQ	food frequency questionnaire
GnRH	gonadotropin-releasing hormone
EQ-5D	EuroQOL five dimension questionnaire
GCP	good clinical practice
HDL	high density lipoprotein
HIIT	intensity interval training
HIPAA	Health Insurance Portability and Accountability Act
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
HRmax	maximum heart rate
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	Insulin- like growth factor-1
LDL	low density lipoprotein
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-6	Interleukin- 6

IV	intravenous
IRB	Institutional Review Board
LHRH	luteinizing hormone-releasing hormone
LPI	last patient in
M-CRPC	metastatic castration-resistant prostate cancer
MI	myocardial infarction
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NFκb	nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf-2	nuclear factor erythroid 2–related factor 2
OS	overall survival
PCWG	Prostate Cancer Clinical Trials Working Group
PDWG	Protocol Development Working Group
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
PSA	prostate-specific antigen
QALY	quality adjusted life years
QOL	quality of life
RCT	randomised controlled trial
RECIST	response evaluation criteria in solid tumours
RM	repetition maximum
RPE	rate of perceived exertion
SAE	serious adverse event
SCC	Site Coordinating Centre
SCT	social cognitive theory
SE	Supervised Exercise group (intervention group)
SDE	Self-directed Exercise group (control group)
SHBG	sex hormone binding globulin
SOC	standard of care
SOM	Study Operations Manual
SS	supplemental study
SSE	symptomatic skeletal related event
TBC	to be confirmed
TBD	to be determined
TIA	transient ischemic attack
TLS	total leisure score
TNM	tumour nodes metastasis
TPB	theory of planned behaviour
TTM	trans-theoretical model
ULN	upper limit of normal
VAS	visual analogue scale
VO2max	maximum oxygen uptake
WHO	World Health Organization

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APPENDICES

1.0 INTRODUCTION

1.1 Exercise as Non-Pharmacologic Adjuvant Therapy for Prostate Cancer

Identifying and evaluating low-toxicity adjuvant interventions that can be combined with standard therapy to improve outcomes for men with prostate cancer is a high priority and has the potential to have a large impact on the clinical and public health burden of prostate cancer. We summarise briefly below promising observational, pre-clinical, and pilot clinical data that support the hypothesis that exercise improves overall survival and health-related quality-of-life (QOL) among men with advanced prostate cancer:

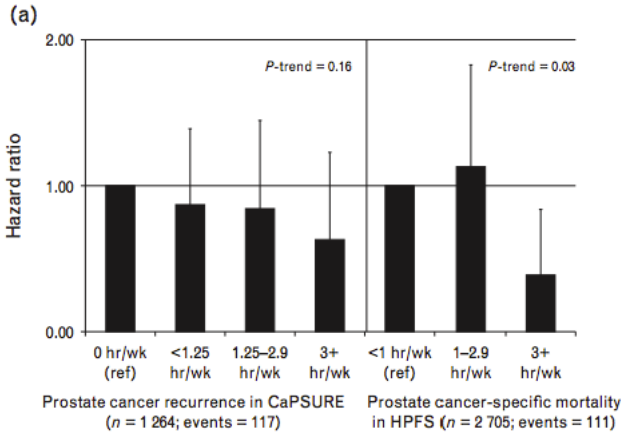


Figure 1. Duration of vigorous physical activity after diagnosis of non-metastatic prostate cancer and risk of prostate cancer recurrence and mortality in two distinct cohorts. Error bars represent the upper bound of the 95% confidence interval (Kenfield SA et al, *J Clin Oncol*, 2011; Richman EL et al. *Cancer Res* 2011).

- Vigorous aerobic exercise after diagnosis was associated with a 60% lower risk of fatal prostate cancer and a 49% lower risk of all-cause mortality among men initially diagnosed with localised disease (Figure 1).[2]
- Among men diagnosed with incident *advanced* prostate cancer (clinical stage T3 or higher), those who reported ≥3 h/wk of non-vigorous activity after diagnosis had a 36% lower risk of death compared to men reporting <1 h/wk (events: 194; HR: 0.64; 95% CI: 0.42, 0.96; *p*-trend: 0.006) (unpublished, please do not cite/quote; Kenfield SA personal communication).
- Loading of bone inhibited growth of metastatic tumours in animal models.[3]
- Resistance exercise and programs with both resistance and aerobic exercise improved physical function and quality-of-life in men without metastases on androgen deprivation therapy (ADT) for prostate cancer.[4,5]
- Treatment-related fatigue is a common side effect in men with advanced prostate cancer,[6,7] and exercise may decrease fatigue and increase adherence to treatment regimens.
- New standard treatments for advanced prostate cancer cause adverse metabolic effects (e.g., weight gain, insulin resistance) that may be avoided or attenuated by exercise.

1.2 Potential mechanisms of exercise influencing prostate cancer tumour biology

Potential mechanisms by which exercise may lower risk of prostate cancer progression, the incidence and progression of comorbidities, treatment side effects, and overall death among men with advanced prostate cancer include:

1) Endocrine - Exercise influences all hormonal systems in the body with key hormones relevant to prostate cancer being testosterone, growth hormone, and insulin-like growth factor-1 (IGF-I). The androgen receptor and its transactivation by ligand are one of the most important determinants of prostate cancer progression. Measurements of serum androgens provide an important biomarker for effectiveness of androgen deprivation and prostate cancer progression. Current studies are inconclusive as to the effects of exercise on serum androgen levels.[8-11] In part, these studies are limited by low patient numbers and inadequate methods for measuring testosterone levels in the low ranges seen in men on androgen deprivation therapy.[12] This is especially true with the newer cyp17 inhibitors, such as Abiraterone.

2) Immune System, Inflammation, and Cytokines – High levels of inflammatory biomarkers are associated with an increased risk of prostate cancer-specific mortality,[13] and exercise is known to lower levels of circulating inflammatory biomarkers (e.g., interleukin- 6 (IL-6)) in elderly populations.[14] In addition, exercise may enhance natural killer cell cytotoxicity and immune surveillance, improving immune defence against prostate cancer. Further, adipokines may also have pro- or anti-oncogenic roles in angiogenesis and cell proliferation. For example, adiponectin has anti-inflammatory effects and its serum concentration is inversely correlated with adiposity.[15] Resistin is associated with insulin resistance through AMP kinase down-regulation. It up-regulates pro-inflammatory cytokines (IL-6, tumour necrosis factor alpha (TNFα)) which act via the nuclear factor kappa-light-chain-enhancer of

activated B cells (NFκb) pathway to increase transcription of proteins involved in cell proliferation, inflammation and anti-apoptosis. In addition, activation of NFκb is implicated in prostate cancer, nuclear expression being associated with nodal metastasis.[16] IL-6 and TNFα are both elevated in the serum of patients with metastatic carcinoma compared to patients without metastases. Interestingly, both are elevated in prostate carcinoma in direct proportion to disease stage,[17] and increases occur at the time of biochemical (PSA) disease progression.

3) Energy Metabolism – Exercise improves insulin sensitivity and glucose metabolism. While ADT in principle is targeting the prostate cancer tumour, the systemic treatment in patients results in a range of alterations associated with metabolic syndrome.[18] One of the earliest changes following ADT, within 2-6 weeks, is a reduction in insulin sensitivity leading to a rise in circulating insulin (hyperinsulinemia); the rise in insulin levels precedes changes in adiposity and increased lipids, sarcopenia, and bone loss.[18,19] High insulin levels are predictive of more rapid progression to CRPC, and poor prognosis.[19,20] Insulin has been shown to have a direct action on prostate cancer growth and progression, and this can be inhibited by blocking insulin action.[21] Additionally, high levels of C-peptide, a marker of insulin secretion, are associated with a more than 2-fold increased risk of prostate cancer-specific mortality.[20] Further, overweight (body mass index (BMI) >25 kg/m^2) men with high C-peptide levels had a more than 4-fold increased risk of prostate cancer-specific mortality compared to normal weight men with low C-peptide levels.

4) Body composition – Cancer and its treatments cause substantial changes in body composition with sarcopenic obesity being a common outcome. This not only results in substantial impediment to functional ability and increased cardio-metabolic risk, but also alteration of adipokine and myokine balance, which may contribute to tumour progression. Exercise increases lean muscle mass and may cause loss of fat mass, thereby improving overall body composition.

5) Epigenetics – Exercise can produce epigenetic modulations that may inhibit tumour cell proliferation, such as altering histone deacetylase pathways.

6) Telomere – Short and/or variable telomere length in the prostate is a prognostic marker among men with prostate cancer. One study among 10 men with localised prostate cancer on active surveillance reported that a lifestyle program that included moderate exercise (as well as diet, stress management, and social support) increased telomere length in blood.[22]

7) Cholesterol - Epidemiological studies have suggested that high levels of cholesterol in the blood are associated with increased risk of prostate cancer and progression of prostate cancer.[23,24] Exercise combined with dietary modification has been demonstrated to substantially reduce total cholesterol as well as improve the ratio of high density lipoprotein to low density lipoprotein cholesterol.

8) Oxidative stress - Exercise has been demonstrated to modulate oxidative stress and improve antioxidant capacity. In a pilot study at the University of California, San Francisco, men with low risk, localised prostate cancer who reported ≥3 hours/week of vigorous physical activity had modulated expression of the nuclear factor erythroid 2–related factor 2 (Nrf-2) mediated oxidative stress response pathway in their normal prostate tissue compared to men who did less exercise.[25] Oxidative stress is hypothesized to play a significant role in the initiation and progression of prostate cancer.[26]

1.3 Randomised Controlled Trials of Exercise Among Men with Prostate Cancer

To date, there have been 21 exercise clinical trials conducted among men with localised prostate cancer treated via radiation, surgery, or watchful waiting and 13 among men with non-metastatic prostate cancer treated with primary ADT;[27-32] however, none have reported on a survival endpoint. Due to the long survival of men with prostate cancer, randomised controlled trials (RCTs) must enrol men with metastatic disease in order to examine a survival endpoint. However, evidence is extremely limited on the effects of exercise among men with metastatic prostate cancer. Only one small pilot study to date conducted in Australia by RU Newton and colleagues included men with metastatic prostate cancer. This 12-week pilot RCT of resistance training versus usual care among 20 men with prostate cancer bone metastases observed no skeletal complications, high attendance (83%) and tolerance (mean=6; scale: 1-7 with 7=highly tolerable), and improved physical function.[32] This trial did not examine the effect of exercise on prognostic biomarkers, progression, or survival, nor did it examine the combined effect of aerobic and resistance exercise. We are aware of one on-going study examining the effect of supervised exercise on cardiorespiratory fitness among men with castrate-resistant prostate cancer (CRPC) on enzalutamide (personal communication LW Jones to JM Chan). **The proposed study would be the first RCT to examine the effect of exercise on overall survival (OS) in men with prostate cancer.**

1.4 Exercise and Quality of Life (QOL) in Men with Advanced Prostate Cancer

As the burden of disease among men with prostate cancer advances, a rapid, significant deterioration in QOL is observed.[33] Bone pain which is reported in up to 80% of patients with metastatic disease throughout their treatment, makes the largest single contributor to QOL deterioration in this population.[34] Other symptoms which compromise QOL include urinary frequency, sexual dysfunction, nausea and vomiting, loss of appetite and dyspnoea.[33] The benefits of exercise training on QOL for men with non-metastatic prostate cancer are well described,[5,35] and include improvements in general QOL and also cancer-specific concerns including fatigue and sexual health. However, whether exercise can improve QOL among men at the end stage of this disease is not known.

Metastatic spread of prostate cancer occurs primarily to sites in the axial skeleton including the femur, pelvis and vertebrae. Metastatic lesions, which are typically osteoblastic, lead to significant bone pain and compromised skeletal quality. Skeletal complications, such as bone fractures, orthopaedic intervention or spinal cord compression, which develop due to bone metastases, result in significant patient morbidity and compromised QOL. Furthermore, compared to those who do not experience a symptomatic skeletal related event (SSE), the occurrence of a SSE is associated with increased patient mortality.[36] A modular multi-modal approach to exercise training involving individualised prescription of exercise to reduce the forces going through the bone has been shown to be safe and feasible in men with bony metastases and not associated with increased risk of pathological fracture.[32] This proposal will test whether exercise training delays time to SSE as well as time to progression of pain and affects measures of pain severity and opiate use. Control or relief of pain and delay or prevention of SSE are both indications for approved therapeutic agents for men with metastatic prostate cancer.[37]

In addition to SSE and pain due to the infiltration of metastatic prostate cancer in bone, men with this disease also experience debilitating cancer-related fatigue and adverse cardio-metabolic health as a side effect of therapy.[6,7] Cancer-related fatigue is a distinct phenomenon from fatigue experienced by healthy individuals and significantly lowers health-related QOL. There are extensive data to support that exercise improves fatigue in men with a lower disease burden.[38-41] This proposal will be the first to examine whether exercise improves or delays onset of cancer-related fatigue in men with metastatic prostate cancer.

1.5 Rationale for Focus on Metastatic Castrate-Resistant Prostate Cancer (MCRPC)

Our overarching objective is to determine the effect of exercise on overall survival among men with advanced prostate cancer. We have chosen to restrict our study population to men with progressive MCRPC because: 1) Men with progressive MCRPC are at high risk for death within a time frame that can be feasibly tested in the setting of a RCT (median OS on treatment = 32[42] to 35[43] months). 2) With the proper use of stratification variables (treatment and study site), it is possible to define a homogenous study population in terms of risk of death; 3) This is the largest group of patients that can be uniformly considered to have advanced prostate cancer and thus provides the largest patient pool for recruitment while also meeting criteria 1 & 2; 4) while new therapies for MCRPC extend life,[44,45] they also cause significant harm to metabolic and cardiac function and health-related QOL which may be attenuated or avoided through exercise; and 5) we hypothesize that exercise will have the largest measurable effect on OS among men with documented evidence of progressing MCRPC (in contrast to men with stable M1 CRPC, non-castrate resistant disease, or non-metastatic disease).

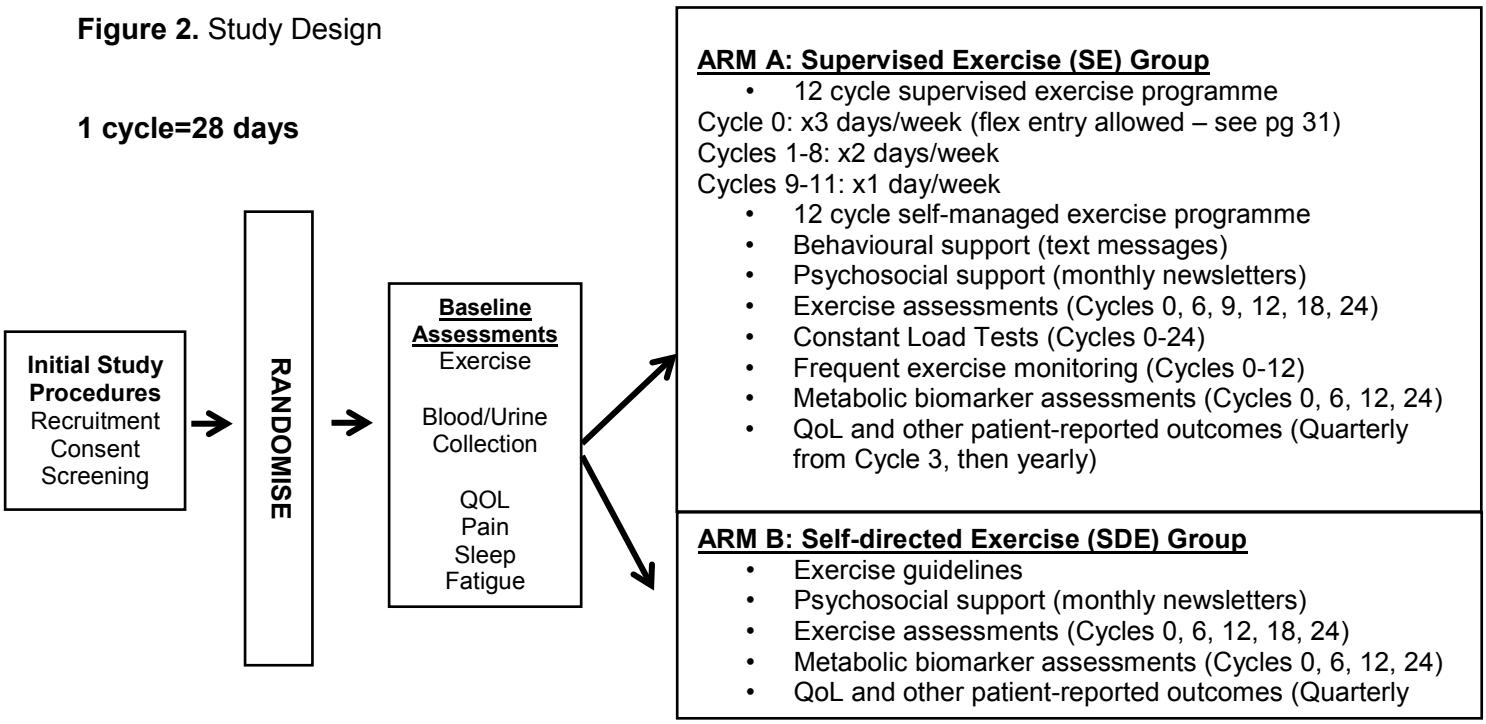
1.6 Rationale for Overall Survival (OS) as the Primary Endpoint

The primary endpoint for this randomised controlled trial will be overall survival (OS). OS was chosen as the primary endpoint because it has clear biological, clinical and public health significance and is a validated endpoint for approval of new treatments among men with MCRPC. Additionally, OS data can be obtained with minimal loss to follow-up through review of medical and death records. The median OS among men with MCRPC is 32[42] to 35[43] months. Thus, OS is a feasible outcome to examine within the budget and timeline of the proposed study.

1.7 Study Design

There is compelling biological and clinical rationale for including exercise in the clinical management of men with MCRPC. We propose that psychosocial support plus exercise will increase OS compared to psychosocial support alone. This will be a phase III RCT of high intensity aerobic and resistance exercise training among men with MCRPC. The first twelve cycles (1 cycle=28 days) of training will be done under supervision which will include a structured period of tapered supervision to self-managed exercise; the training program will be self-maintained with text messages and in-person sessions to support self-maintenance for an additional 12 cycles.

Figure 2. Study Design



2.0 OBJECTIVES

Primary Objective:

2.1 To determine if high intensity aerobic and resistance training plus psychosocial support increases overall survival compared to psychosocial support alone in patients with metastatic castrate-resistant prostate cancer.

Secondary Objectives:

2.2 To compare progression free survival between the intervention and control groups.

2.3 To compare the time to first occurrence of a symptomatic skeletal-related event between the intervention and control groups.

2.4 To compare time to progression of pain, degree of pain, and opiate use between the intervention and control groups.

2.5 To compare change in levels of inflammation, energy metabolism, and androgen metabolism biomarkers between the intervention and control groups over time.

2.6 To determine whether biomarkers of inflammation, energy metabolism, and androgen metabolism are associated with overall survival and explore the extent to which these biomarkers mediate the hypothesized association between exercise and overall survival.

2.7 To compare physical and emotional quality of life between the intervention and control groups

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- Patients must be mCRPC. This is defined as adenocarcinoma of the prostate with systemic metastatic disease despite castrate levels of testosterone (<50 ng/dL) due to orchiectomy or LHRH agonist.
    - Patients must have one or more of the following to be considered mCRPC
        - Metastatic Disease Progression: >20% increase in the sum of diameters of measurable lesions from the time of maximal regression or appearance of one or more new lesions.
        - Bone Scan Progression: Appearance of one or more new lesions on bone scan attributable to prostate cancer.
        - PSA Progression: PSA ≥2 ng/ml that has risen serially on at least two occasions, each at least one week apart (PSA1 < PSA2 < PSA3).
- Castrate levels of testosterone must be maintained while on study. Be on androgen deprivation therapy (ADT) with a GnRH agonist/antagonist or prior bilateral orchiectomy. All patients will be required to be on ADT during the study period or have had a prior bilateral orchiectomy. Men with small cell neuroendocrine tumours or features of small cell disease are not eligible.
- At enrolment, patients must fit into one of the following 4 categories:

    1. Treatment naïve for mCRPC (have not yet started approved therapies for CRPC ie: Abiraterone/Enzalutamide/Apalutamide/Docetaxel; less than 4 weeks on approved therapies is still considered to be treatment naïve)

    Or

    2. Receiving Abi/Enza/Apa for mCRPC AND responding or stable (PSA values must be stable or declining after at least 4 weeks since starting Abi/Enza/Apa for mCRPC)

    Or

    3. Patients with PSA progression while on Abi/Enza/Apa are eligible as long as they are asymptomatic AND there is no intent on starting chemotherapy within 6 months

    Or

    4. Patients treated with Docetaxel as first line therapy for mCRPC who are asymptomatic without ANY evidence of progression

    Or

    5. Patients may have progressed following Docetaxel first line and are now receiving treatment with Abi/Enza/Apa. These patients must absolutely be responding or stable (PSA values must be stable or declining after starting Abi/Enza/Apa treatment) and have an expected life expectancy of more than 1 year.

- ≥4 weeks since any major surgery and fully recovered.
- Halabi Nomogram score <195[1] (Risk Category rated as low or intermediate risk)
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Patients must be able to travel to one of the study-designated exercise facilities up to three days per week for four weeks during cycle 0, two days per week for cycles 1-8 (32 weeks) and once per week for cycles 9-11 (12 weeks). In addition, patients must be able to attend exercise testing visits as outlined in the Table 1.
- Required Initial Laboratory Values:
    - Absolute neutrophil count (ANC) ≥ 1500/uL
    - Platelet count ≥ 100,000/uL
    - Creatinine ≤ 1.5 x upper limits of normal
    - Bilirubin ≤ 1.5 x upper limits of normal
    - Aspartate aminotransferase (AST) ≤ 1.5 x upper limits of normal
    - Serum testosterone ≤ 50 ng/dL

- Medical clearance to undergo a symptom-limited cardiopulmonary exercise test (CPET) and vigorous aerobic and resistance exercise training.
    - Appendix 8: Certain medical questions with 'YES' responses require cardiologist clearance or physician clearance to participate. See SOM for details.
- Successfully pass the screening CPET by achieving:
    - Volitional exhaustion (RPE ≥ 9 using the Borg 0-10 RPE scale) in the absence of any cardiorespiratory abnormalities.
        - If cardiorespiratory abnormalities are identified, please refer the patient to his managing physician for further assessment and diagnosis.

      Note: To assist practitioners with delivering valid CPET assessments, patients nearing exhaustion should achieve a respiratory exchange ratio (RER) of ≥1.1.
      RER is not a criteria of the test. This objective measure should only be used to assist practitioners with patient management and decision-making.
- Exercise Coordination Centre (ECC) review and approval of subject's screening bone scan/ areas with bone metastases.
- Subject is willing and able to use the technological aspects of the trial.
- The subject is fluent in the language as designated by the institution at which he would be enrolled.

3.2 Exclusion Criteria

- Previous radiographic or clinical progression (PSA progression is permitted) while on treatment with abiraterone, enzalutamide, apalutamide, or a combination.
- Previously identified small cell neuroendocrine tumours or pure small cell carcinoma of the prostate, based on a prior biopsy of the prostate.
- Brain metastases (brain imaging is not required)
- Previous and/or concurrent treatment with other anti-cancer treatments is permitted. Patients are allowed to be treated with chemotherapy during the duration of the trial. Patients who have received chemotherapy as part of initial androgen deprivation therapy for metastatic castration sensitive disease are eligible.
- Currently receiving experimental treatment with non-approved drugs at the time of enrolment. Patients must undergo a 28-day washout between last dose and screening CPET.
- Poorly controlled hypertension. During screening ≥2/3 of readings must be < 160/90, regardless of whether on a regimen of anti-hypertensive therapy or not.
    - If patient is currently taking hypertensive medication(s)/therapy, please indicate medication and include in the Treatment and Concomitant Medications Log (SOM: Appendix 11).
- Current congestive heart failure (New York Heart Association Class II, III or IV)
- Recent serious cardiovascular events (within 12 months) including, but not limited to, transient ischemic attack (TIA), cerebrovascular accident (CVA), or myocardial infarction (MI).
- Medical condition such as uncontrolled infection or cardiac disease that, in the opinion of the physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a currently active second malignancy other than non-melanoma skin cancer. Patients are not considered to have a currently active malignancy if they have completed necessary therapy and are considered by their physician to be at <30% risk of relapse at time of assessment.
- Psychiatric illness, which would prevent the patient from giving informed consent or adhering to the study protocol.
- Serious or non-healing wound, ulcer, or bone fracture.
- Known spinal cord compromise or instrumentation due to metastatic disease in the mCRPC state. Radiation therapy for metastatic disease is allowed.
- Peripheral neuropathy ≥grade 3.
- Men participating in vigorous aerobic exercise for more than 60 minutes per week or structured

resistance exercise two or more days per week (seek ECC approval before exclusion).

- Experiences shortness of breath, chest discomfort, or palpitations when performing activities of daily living (patient with these symptoms can participate in the study with cardiologist clearance)
- Ongoing restriction of physical activity with physician documentation
- Has chest pain brought on by physical activity (patient can participate in the study with cardiologist clearance)
- Has developed chest pain in the past month (patient can participate in the study with cardiologist clearance)
- Moderate-to-severe bone pain (i.e., National Cancer Institute's Common Terminology Criteria for Adverse Events grade 2-3 bone pain).
- Men who do not complete the baseline lifestyle and quality-of-life questionnaires and 3-days of diet diaries or country-specific FFQ will not be eligible

4.0 SCREENING, RANDOMISATION, STRATIFICATION, BLINDING

4.1 Informed Consent

All patients must willingly consent after being informed of the procedures to be followed, the experimental nature of the intervention, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and its consent form are required. Informed consent is required before any study-specific procedure is performed. Patients who sign the study consent form should be entered into the screening database.

4.2 Screening

Patients who are potentially eligible for GAP4 and sign the study Informed Consent should be given a site specific screening ID, and entered into the database. Participants will continue to be screened for the trial until 866 participants have been randomised.

4.3 Enrolment

A physician must determine whether a patient is eligible for GAP4 based on the inclusion criteria. The screening CPET must occur within 14 days of Day 1, Cycle 0 (Baseline). Prior to randomisation, approved GAP4 institutions must have Site Coordination Centre (SCC) approval and enter all of the following information into the following online database forms:

Consenting

Subject Identification

Patient-completed Demographics, Exercise Screening, and Questionnaires Parts 1-4

Physician Clearance Form

Eligibility for CONSORT Reporting and Signed Eligibility Criteria Checklist

When the patient successfully completes screening procedures and is eligible for enrolment, a patient identification number (separate from the patient screening ID) will be assigned. Participants will continue to be enrolled onto the trial until 866 participants have been randomised.

4.4 Randomisation

After SCC approval, patients will be randomised in a 1:1 ratio to intervention (Supervised Exercise/SE) group or control (Self-directed Exercise/SDE) group, stratifying by treatment status at time of randomisation and study site. Randomisation will be performed through the study database but maintaining concealment from patients and recruiting staff, upon which time a Study ID will be assigned to the subject.

4.5 Stratification

Patients will be stratified by study site and treatment status at the time of registration: 1) Patients who are treatment naïve or stable on Abiraterone/Enzalutamide/Apalutamide or 2) Patients who are on/received first line chemo OR progressing on first line Abiraterone/Enzalutamide/Apalutamide. Patients treated with radium-223 will need medical monitoring review for correct stratification placement. Previous and/or concurrent treatment with other anti-cancer therapies is permitted. Patients who have previously received sipuleucel-t, meet study eligibility, and are not on the treatments listed above, are not considered on treatment. Patients

receiving experimental treatment with non-approved drugs at the time of enrolment are not eligible. Patients receiving treatment with combinations of approved drugs are eligible, provided documentation and clearance by the SCC.

Allocation within strata will be carried out using blocked randomisation in random blocks of 2, 4, or 6.

4.6 Blinding

Due to the nature of the intervention being tested (exercise), investigators, research staff and patients cannot be blinded to the patients' randomisation assignment. However, the laboratory processing patient samples and the statistician performing the *a priori* specified primary and secondary analyses will be blinded.

5.0 CLINICAL PROCEDURES

Guidelines for Pre-Study Testing:

All laboratory tests that are specified in the eligibility criteria (absolute neutrophil count, platelet count, creatinine, bilirubin, aspartate aminotransferase, PSA, serum testosterone) as well as blood-based markers that are part of the Halabi score should be completed within 28 days before Cycle 0, Day 1 (see footnote #7). The CPET must be completed within 14 days of Cycle 0, Day 1. Participants are randomised after the CPET.

Table 1. Summary of assessments. One cycle = 28 days. (Next page)

Table 1 Summary of Assessments	Screening	On-Treatment Study Period[1]																									Off-Treatment
		Cycle 0: Baseline[2]	Supervised Exercise									Transition			Self-managed exercise program												Follow-up Period
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Informed Consent	X																										
Randomisation	X[4]																										
Clinical History																											
Medical history[&]	X																									X	
Tumour histology	X																										
Medication/Tx history	X				X			X			X			X			X			X			X			X	
Body Measurements																											
Height	X[3]																										
Weight, waist, hip circumference	X[3]							X[5]						X[5]						X[5]						X[5]	
Lab Studies																											
CBC w/diff, blood chemistries[6]	X[7]				X[6]			X						X[6,8]			X[6]			X[6,8]			X[6]			X[6,8]	
Fasting Lipid Profile (LDL, HDL, Triglycerides), fasting Glucose, HbA1c		X						X																			
Efficacy																											
Overall survival status, Disease progression, Symptomatic-skeletal event[9]								X[9]						X[9]						X[9]						X[9]	Twice yearly[9]
WHO analgesic scale	X				X			X			X			X			X			X			X			X	Once yearly[9]
CPET with ECG[3]	X[10]							X[11]						X[11]													
ARM A - Constant Load test[10]		X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ARM A - 1-RM Strength test		X[10]						X[11]			X[11]			X[11]						X[11]						X[11]	
ARM B - 1-RM Strength test		X[10]						X[11]						X[11]						X[11]						X[11]	
400 m walk test		X[10]						X[11]						X[11]						X[11]						X[11]	
Safety																											
Medical Clearance(s)[12]	X							X						X						X							
Vital signs[13]	X[3]	X						X						X						X						X	
ECOG performance status	X				X			X			X			X			X			X			X			X	
Bone pain at exercise visits		Assessed at each supervised exercise visit using VAS																									
Adverse events[14]	X[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications[15]	X[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1 Summary of Assessments (Continued)	Screening	On-Treatment Study Period[1]																								Off-Treatment
		Cycle 0: Baseline[2]	Supervised Exercise								Transition			Self-managed exercise program												
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Metabolic Research Studies																										
Research blood (fasting)		X[16]						X[17]						X[17]												X[17]	
FFPE tumour specimens		Request[18]																								
Urine specimens		X						X						X												X	
Patient Report Outcomes																										
Appx 5 Demographics & Health History Questionnaire	X[19]																									
Appx 8 Exercise Screening Questionnaire	X																									X[21]
FACT-G, EPIC-26, FACIT-Fatigue, EORTC QLQ-C30, STAI, CES-D, PSQI, falls[20]	X[19]				X			X			X			X			X			X			X			X	X[21]
BPI-SF and EQ5D [20]	X[19]							X						X						X						X	X[21]
Exercise questions modified from baseline, Modified Godin exercise scale, memory, exercise motivation[20]	X[19]							X						X						X						X	
Diet[20]	X[19]													X												X	
Cost of Participation								X						X													

TABLE ABBREVIATIONS:
EMR: electronic medical record; CPET: Cardiopulmonary Exercise Test; ECG: Electrocardiogram; SOC: Standard of Care; ECOG: Eastern Cooperative Oncology Group; PSA: Prostate Specific Antigen; EG: Exercise Group; FFPE: formalin-fixed paraffin-embedded; PFS: Progression-free survival; OS: overall survival; SSE: symptomatic skeletal-related events; BPI-SF: Brief-Pain Inventory Short Form; FACT-G: Functional Assessment of Cancer Therapy-General; FACIT: Functional Assessment of Chronic Illness Therapy; EPIC-26: Expanded Prostate Cancer Index Composite Instrument, EQ5D: Euro-Quality of Life 5-dimension; STAI: State-Trait Anxiety Inventory; CES-D: Centre for Epidemiologic Studies Depression

FOOTNOTES:
[1] The study period is comprised of cycles. Each cycle equals 28 days.
[2] Day 1 of the study period (baseline) is the same for each arm. It is defined as Day 1, Cycle 0 when the remainder of the baseline physical capacity and function tests are completed. Men are randomised prior to this day. This day is also the first day of training in the Supervised Exercise/SE (intervention arm). The patient is to be told which arm they are randomised into ***after*** Baseline testing is completed, which is at the end of Day 1, Cycle 0 testing – where "next steps" in the study are explained.
[3] Assessed at screening visit with exercise physiologist, trainer, etc., which must occur within 14 days prior to Day 1, Cycle 0. Concomitant medications are recorded by clinical research coordinator in REDCap and exercise physiologist/trainer will review with patient at the CPET screening visit. The baseline anthropometric measurements do not need to be

re-assessed if these measurements were already taken within the same week (prior 6 days).
[4] Patients are randomised after successfully completing the CPET and prior to Day 1, Cycle 0. Current treatments must be submitted to ensure correct stratification.
[5]Follow-up measurements will be assessed by the exercise physiologist, trainer, etc.
[6]Includes: CBC with differential, total bilirubin, ALT, AST, ALP, Albumin, Sodium, Potassium, serum Calcium, Magnesium, BUN, Creatinine, Glucose, LDH, PSA, Testosterone, haemoglobin. All required at Cycle 6 only. Quarterly assessment can be obtained via SOC, For SOC, record the first instance of blood assessments obtained as SOC for each patient after Day 1 of the quarterly Cycles: 3, 9, 12, 15, 18, 21, and 24. If no SOC labs are ordered within the quarter, please indicate on blood assessments database form. (SOC Example: Patient starts Cycle 9, CBC w/ diff ordered for pt at Cycle 10, record values under Cycle 9 eCRF. If the CBC with diff is ordered again in the same quarter (e.g. Cycle 11), there is no need to record)
[7]All laboratory tests that are specified in the eligibility criteria (haemoglobin, ANC, platelet count, creatinine, bilirubin, AST, PSA, serum testosterone) and blood-based markers which are part of the Halabi score (PSA, LDH, albumin, ALP) should be completed within 28 days before Day 1, Cycle 0. Non-screening labs can be done at Cycle 0, with research bloods (participants are randomised after the CPET). For treatment naïve or stable (Groups 1 and 2): prefer 28 days or less, but will allow up to 42 days indicated as a deviation. For patients with PSA progression on abi/enza/apa or patients treated with docetaxel as first line therapy for mCRPC (Groups 3 and 4 and 5): must be completed within 28 days or less.
[8]The Halabi variables (PSA, LDH, albumin, haemoglobin, and ALP) are required at Cycles 12, 18, and 24. If site will incur a cost to order these assessments at Cycles 18 and 24, please record the values for these variables from the closest date to these time-points ordered as SOC.(SOC see footnote #6)
[9]Per review of medical records or other documentation by research assistant followed by confirmation by site PI. Mortality data will be collected through medical records, death records, and other resources every 6 months during the on-treatment and follow-up periods. If the participant is lost to follow-up, we will contact next of kin or alternate contact. Death certificates will be requested along with access to the medical records related to the death, and centrally reviewed to determine cause of death.
[10]The CPET is assessed prior to and within 14 days of Day 1, Cycle 0. *The CPET should only be performed after all other screening procedures are completed and verified as eligible*. The remainder of the physical function and strength tests (i.e., one repetition maximum chest press, leg press and seated row) will be carried out either on the day of the CPET *or* at Day 1, Cycle 0 (see protocol). Constant Load tests during follow-up will occur within 7 days *on or after* Day 1 of the Cycle.
[11]Exercise assessments will occur within 7 days *on or after* Day 1 of the Cycle.
[12]Medical clearance(s) for continued participation must be documented by the treating physician every 6 months (SOM: Appendix 9) in the absence of any SAEs. (See "Safety Assessments on page 4)
[13]Blood pressure and heart rate are also assessed at the start of every session for patients in the SE (intervention) arm who are known to have high blood pressure, history of unstable blood pressure, symptomatic, or reports new treatment. If 2/3 readings demonstrate the pressure to be >160 OR >90 at the time of the session, exercise will be held on that day.
[14]Continuously reported from informed consent until 28 days after Cycle 24, Day 1. All adverse events (AE) should be followed to their resolution, until the PIs assess them as stable, irreversible, or until the patient refuses further follow up, whichever comes first. AEs are assessed by the exercise physiologist, trainer, etc. at on-site exercise visits and in all subjects (in person or by phone) on a monthly basis. AE events will be recorded on the AE form and logged in REDCap. AE assessment will include bone pain.
[15]Medications will be reviewed with the patient once a month, either in person or by phone call. Medications will be logged and entered into the REDCap database.
[16] Sec 8.3: Baseline blood collection will occur after the patient passes the baseline CPET, and will occur before or on Day 1, Cycle 0, before the remainder of the exercise tests are performed and at least 48 hours after any vigorous activity including the screening CPET visit
[17]Sec 8.3: Follow-up blood collection will occur prior to completing the exercise tests on that day (see footnote #11), and at least 48 hours after any vigorous activity. If it cannot be completed on that day, it must be completed within 7 days after Day 1 of the Cycle, at least 48 hours after any vigorous activity.
[18]Request access to available archival formalin-fixed paraffin-embedded (FFPE) tumour blocks or tumour slides from consenting patients for future biomarker analyses.
[19]The baseline surveys or FFQ will be completed within 28 days prior to the screening CPET and used as the baseline assessments
[20]Appendix 6, 20-27, 29, 31, 33. All follow-up surveys and FFQ will be completed within 7 days before the exercise assessment, except for Appendix 20, 24, and 33, which are completed on paper at the visit or by mail.
[21]Selected assessments will be administered during the follow-up period on a yearly basis. If no response is received from the participant and medical records do not indicate death, we will follow up with the next of kin or alternate contact.
[&]New conditions diagnosed on-study are recorded during the on-study period.
Other Time restrictions not mentioned in the footnotes:
*A minimum of 48 hours recovery will be implemented between resistance training or HIIT of the same muscle group using a split program design.

5.1 Clinical Assessments

5.1.1 Demographic Information

Demographic information (e.g., date of birth, race, marital status, education) will be recorded at Screening via questionnaire.

5.1.2 Clinical History

Relevant medical history, including current disease, other pertinent clinical conditions, and information regarding underlying diseases will be recorded at Screening (see Medical History section in Appendix 5).

The following items should be reported:

- **Medical History:** includes history of other disease processes (active or resolved) not related to the diagnosis of prostate cancer, concomitant illnesses
- **Prostate Cancer History:** histology of the tumour, date of the histological diagnosis, clinical Tumour Nodes Metastasis (TNM) stage at diagnosis, Gleason score of the tumour at diagnosis (biopsy and surgical, if available)
- **Tumour histology:** Adenocarcinoma, adenocarcinoma with small cell neuroendocrine features, small cell neuroendocrine. Men with small cell neuroendocrine disease or features are not eligible.
- **Comprehensive treatment history:** Select treatment information for prostate cancer and the start and stop dates.
- **Current sites of metastasis:** Lymph nodes, bone, liver, lung, other, or none.

5.1.3 Physical Exam

We request a medical clearance from their general practitioner (MD) or treating oncologist to confirm the patient is physically and psychologically able to participate in the trial. We leave it up to their doctor to determine if they require a physical exam. Weight, Height, Waist Circumference, Hip Circumference and Vital Signs should be measured as per the schedule of assessments (see Table 1). Descriptions and instructions pertaining to these assessments are provided in the SOM.

5.1.4 Performance Status

The ECOG performance status scale will be used (SOM: Appendix 7) and assessed by authorised site personnel (the physician at the time of physician clearance or exercise physiologist/trainer, if regularly-performed task).

5.1.5 Concomitant Medications/Therapies

Standard medical treatment as applicable is allowed. Additionally, any therapy initiated after randomisation for the treatment of MCRPC should be preceded by documented clinical evidence of disease progression, a SSE, pain, or other clinical indication. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF. All concomitant medication and concurrent therapies will be documented from informed consent until 28 days after Cycle 24 (end of intervention): name, indication for administration, and dates of medication or therapy (SOM: Appendix 11).

5.1.6 Opiate Use (see WHO analgesic scale in SOM: Appendix 28)

Opiate use will be obtained every 3 cycles through medical record review. The WHO analgesic score will be used to grade opiate use according to the following criteria; 0 = no use; 1 = use of non-opiate analgesics (eg, non-steroidal anti-inflammatory drugs, acetaminophen, antidepressants, and agents targeting neuropathic pain; 2 = use of weak opiates for moderate pain (e.g., codeine and tramadol); 3 = strong opiates for severe pain (e.g., morphine and fentanyl).

5.2 Exercise Laboratory Measurements (SOM: Appendices 14-16)

The following exercise assessments will be completed in both the intervention and the control group at screening/baseline (see note) and within 7 days on or after day 1 of Cycle 6, 12, 18 and 24, subject to location of bone metastases.

NOTE: The first cardiopulmonary exercise test will be completed during the screening period to ensure eligibility. The results of the screening measure will be used as the baseline result. Subsequent assessments will be completed over two days (Day 1: Cardiopulmonary exercise test; Day 2: 400m Walk test, 1RM test) at least 48 hours apart for Cycle 6 and Cycle 12, and over 1 day for Cycles 18 and 24.

1. Cardiopulmonary Exercise Test (During screening 2-14 days prior to Cycle 0, and within 7 days on or after Day 1, Cycle 6 and 12)
2. 400m Walk Test (completed on Cycle 0, and within 7 days on or after Day 1, Cycle 6, 12, 18, and 24)
3. Strength assessment (completed on Cycle 0, and within 7 days on/after Day 1, Cycle 6, 12, 18, and 24)
    a. 1RM Chest Press
    b. 1RM Leg Press
    c. 1RM Seated Row
    d. 1RM Leg Extension

Aerobic fitness and muscle strength will be monitored in the exercise intervention group only to inform exercise prescription and progression throughout the supervised exercise program. The following exercise monitoring assessments will be completed, subject to location of bone metastases.

1. Strength assessment (completed within 7 days on or after Day 1 of Cycle 9)
    a. 1RM Chest Press
    b. 1RM Leg Press
    c. 1RM Seated Row
    d. 1RM Leg Extension
2. Constant Load Exercise Test (completed within 7 days on or after Day 1 of Cycle 0-24/Off-Study Visit)

Full details of all assessments can be found in SOM: Appendix 13: Exercise Physiologist Manual #1 – Exercise Testing Instructions.

5.2.1 Cardiopulmonary Exercise Test with Electrocardiogram (ECG)

Maximal oxygen uptake (VO2max) will be measured using a cycle ergometer-based CPET during screening (2-14 days prior to Cycle 0, Day 1) and within 7 days on or after Day 1 of Cycles 6 and 18. Gas exchange will be measured by indirect calorimetry. Participants must receive medical clearance to complete testing. For any participants currently under the management of a cardiologist, their additional clearance is required. Pre-test resting heart rate, blood pressure, respiratory rate and ECG readings must be recorded. A standard 12-lead ECG (with a 10-second rhythm strip) will be collected prior to, during, and for 5-minutes after all CPETs. The pre-exercise ECGs will be collected after the patient has rested quietly and is awake in a fully supine (or semi-recumbent, if supine is not tolerated) position for 10 minutes, and prior to any blood draw collection. Subsequent pre-exercise ECG readings should be collected with the patient in the same position (e.g., fully supine or semi-recumbent).

The exercise test will last approximately 8-12 minutes, commencing at a light cycling load that will progress incrementally during the test. A ramped protocol, starting at 20W (linearly increasing at 10 W/min or 15 W/min) as suited to the participant should be completed. A pedalling frequency of 70-80 RPM should be maintained during the test. The test is terminated when cycling speed falls below 50RPM despite motivation, due to physical fatigue. Participants should achieve volitional exhaustion (RPE ≥ 9 using the Borg 0-10 RPE scale) after 8 (or more) minutes, in the absence of any cardiorespiratory abnormalities to indicate that maximal load has been

achieved. Objectively, to assist practitioners with delivering valid CPET assessments, patients nearing exhaustion should be achieving a respiratory exchange ratio (RER) near ≥1.1; however RER is not a required criteria of the test. The test concludes with participants completing 5 minutes cycling at 10W. Blood pressure, heart rate, RPE and ECG will be measured at regular intervals throughout the test and during recovery. If the patient or exercise physiologist accidentally or incorrectly stops the test prior to volitional exhaustion, a repeat test can be provided within the same session after a 10 minute rest, providing the patient, exercise physiologist and supervising medical doctor are satisfied that a second trial is likely to be successful.

5.2.2 400m Walk Test

The 400m walk test is a self-paced, submaximal exercise test. The time taken to complete the 400m course correlates well with VO_2max and will provide a surrogate measure of aerobic fitness and physical function during the intervention. Participants will be required to move as fast as they can along a 20m course, demarked by two cones, until they have completed 10 laps of the course (400m). The time taken to complete the test will be recorded. Heart rate will be measured pre-test, immediately post-test, 1-minute post-test and 2-minutes post-test using a heart rate monitor. At the end of the test participants will complete a lap of slow walking as part of active recovery.

5.2.3 Strength Assessments

Strength assessments will comprise one repetition maximum chest press, leg press, seated row and leg extension. The 1-RM is defined as the highest load that can be lifted through full range of movement at one time. Participant suitability to perform each test will be dependent on the site of the metastasis (see Table 2). The decision to either complete or not complete 1RM testing at each site will be decided by the exercise physiologist performing the test and the exercise coordinating centre in consultation with the participant's treating physician. A detailed description and instructions of how to perform the chest press, leg press, seated row and leg extension are provided in the SOM.

Table 2. Modification to 1 Repetition Maximum Testing by Site of Bone Metastases

Metastases site	**Body Region to Target**		
	Upper body	Trunk	Lower body
Pelvis	√	√	√ [b]
Lumbar spine	√	-	√
Thoracic spine, sternum and/or ribs	√ [a]	-	√
Femur	√	√	√ [b]
All regions	√ [a]	-	√ [b]

Systematic approach to resistance exercise selection for prostate cancer with bone metastases (Cormie et al., (2013).
√ = target exercise region
[a] = Exclusion of shoulder flexion /extension/abduction/adduction; inclusion of elbow flexion/extension
[b] = Exclusion of bilateral hip extension/flexion; inclusion of knee extension/flexion

5.2.4 Constant Load Exercise Test (Arm A only)

The constant load exercise test is a short exercise test that is performed on a cycle ergometer. The patient will complete a graded warm-up for 3 minutes, prior to completing the actual test: cycling for three minutes at a pre-set level of effort (70% of the maximal workload of their first CPET) while maintaining 70-80 RPM. After the test, the patient will commence recovery by cycling for 4 minutes at 10 watts. The patient's rating of perceived exertion, maximum heart rate, average heart rate and heart rate recovery will be measured. These results will be used to inform the effectiveness of the aerobic program to ensure patient fitness and management is effective (SOM: Appendices 13-14).

5.3 Laboratory Measurements

Blood tests will be completed at screening if needed for determining eligibility. Blood for metabolic research studies will be obtained at baseline (Cycle 0, Day 1), and Cycles 6, 12, and 24 (Table 1). Complete details on sample collection and shipment procedures for research samples can be found in SOM: Appendices 17-19. Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following adverse events.

5.3.1 Haematology/Blood Chemistry

These tests are typically standard of care (SOC) for this patient population. The clinical research coordinator will record these and any other assessments ordered by the MD not pertaining directly to the study assessments throughout the study period, when available.

- Haemoglobin
- Platelet count
- Red blood cell count
- White blood cell count
- White blood cell differential
- Total bilirubin (if >1.5 x ULN, include analysis of direct and indirect bilirubin)
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)
- Alkaline phosphatase (ALP)
- Albumin
- Sodium
- Potassium
- Calcium (serum)
- Magnesium
- Blood urea nitrogen (BUN) or urea
- Creatinine
- Glucose
- Lactate Dehydrogenase (LDH)
- Prostate specific antigen (PSA)
- Testosterone

Sites may perform additional local haematology and/or blood chemistry assays for the purposes of planning therapy administration, therapy dose modification, or monitoring adverse events.

5.3.2 Clinical Requests

Fasting Lipid profile (HDL, LDL, and Triglycerides), fasting glucose, and HbA1c will be requested at local sites at baseline and Cycle 6. Halabi measurements (PSA, LDH, albumin, haemoglobin and ALP) will be requested at local sites at screening (part of eligibility criteria) and cycles 6 and 12.

5.3.3 Additional blood markers

Interleukin-1 beta (IL-1β), IL-6, TNFα, Interleukin-2 (IL-2), adiponectin, c-peptide, insulin, sex hormone binding globulin (SHBG), CRP and IGF-1 will be performed for time point's baseline and Cycle 6. Testosterone, dihydrotestosterone, androstenedione, DHEA, 17-hyroxypreogesterone, 17-hydroxypregnenolone, and progesterone will be assessed at baseline only.

5.3.4 Diagnostic archived tumour specimens

Consent to obtain archived prostate cancer tumour samples or slides will be requested from all participants.

5.4 Questionnaire Data

Patients will complete these forms within 28 days prior to the screening CPET and 7 days prior to Day 1 of Cycle 3, 6, 9, 12, 15, 18, 21, 24, and then on a yearly basis. (See Table 1. Summary of Assessments). Dietary intake will be assessed prior to the screening CPET and 7 days prior to Day 1 of Cycle 12 and 24.

Questionnaires to be completed will include:

- **Brief-Pain Inventory Short Form (BPI-SF): (screening, cycles 6,12,18 and 24)**(Appendix 20) A 9-item tool used to assess the severity of pain and the impact of pain on activities of daily living over a recall period of 24 hours. Pain severity is assessed across four sub-scales; 'worst pain', 'least pain', 'average pain' and 'current pain'. A pain score for each subscale is presented separately. Scales are rated on a scale of 0 to 10 (0 = no pain; 10 = pain as bad as one can imagine). A composite score for pain severity is calculated as the mean of the four severity items. Question 9 comprises a 7-item interference scale. Questions assess the level to which pain interferes with general activity, walking, work, mood, enjoyment of life, relations with others and sleep on a scale of 0 to 10 (0 = does not interfere; 10 = completely interferes). Mean interference score will be calculated as an average of the seven subparts of question 9 where at least four of the seven items are completed. The BPI-SF can be completed in 10 minutes.
- **Functional Assessment of Cancer Therapy-Prostate (FACT-G):** (Appendix 21) The FACT-G consists of 27-items. We will be assessing the social/family wellbeing domain of the FACT-G only, while the full EORTC QLQ-C30 will be the primary QOL assessment (described below). This can be completed in 5 minutes.
- **Expanded Prostate Cancer Index Composite (EPIC-26):** (Appendix 22) The EPIC questionnaire focuses on 5 domains: urinary incontinence and irritation, bowel, sexual, and hormonal, with function-specific bother in each domain. Resulting domain scores for the EPIC-26 is on a 0 to 100 scale; higher values representing a more favourable HRQOL. Complete reliability and validity evaluations were conducted for EPIC and are previously described.[46]
- **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Subscale**: (Appendix 23) The FACIT-fatigue subscale contains 13-items assessing the consequences of fatigue. Each item is rated on a 5-point Likert scale ranging from 0 = not at all to 4 = very much. The FACIT-Fatigue can be completed in 5 minutes.
- **EuroQOL 5-dimension questionnaire (EQ-5D)**: **(screening, cycles 6, 12, 18 and 24)** (Appendix 24) The EQ-5D evaluates the health state of an individual. The questionnaire assesses health related QOL across five socially relevant domains: i) mobility, ii) self-care, iii) usual activities, iv) pain-discomfort, and v) anxiety-depression. Participants must grade their own current level of function in each domain according to three levels of disability (severe, moderate or none). Furthermore, participants self-assess their own health status on an accompanying visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Value sets are used to weight each of the 245 health states that can be ranked and transformed to a single utility score. The utility score is an expression of Quality Adjusted Life Years (QALY). A QALY places a weight on time in different health states, providing a composite score of life expectancy and quality of remaining years and is therefore a measure of quality of life adjusted survival. The most recent five-level version (EQ-5D-5L) will be used. The EQ-5D-5L can be completed in 10 minutes.
- **EORTC QLQ-C30:** (Appendix 25) The EORTC QLQ-C30 consists of 30 questions developed to assess the quality of life of cancer patients. It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included. The QLC-C30 was designed to be cancer-specific, multidimensional in structure, appropriate for self-administration, and applicable across a range of cultural settings.

- **Centre for Epidemiologic Studies Depression Scale (CES-D)** (Appendix 26) (20 questions) and **Spielberger State-Trait Anxiety Inventory for Adults** (Appendix 27) 40 questions at baseline and 20 questions at subsequent assessments), are standard questionnaires to assess depression and anxiety. These questionnaires together can be completed in 15 minutes.

- **Godin Leisure Time Physical Activity Questionnaire:** (Appendix 29) Self-administered, four-item questionnaire designed to measure an individual's leisure-time activity during a typical week. Participants are asked to consider the number of occasions they spend per week, of at least 15 minutes duration, in strenuous, moderate and mild exercise. A total leisure score (TLS) is calculated as the sum of weekly frequencies of strenuous, moderate and vigorous intensity activity by their corresponding MET values: *[TLS = (9 METs x strenuous activity time) + (5 METs x moderate activity time) + (3 METs x light activity time)].* The questionnaire also asks participants to consider how often they engage in activity long enough to work up a sweat with respondents choosing from the options: *"often", "sometimes"* or *"never/rarely".* The modified Godin questionnaire can be completed in 1 minute.

- **Pittsburgh Sleep Quality Index (PSQI):** (Appendix 31) This 10 question assessment will be used to assess sleep quality and sleep habits and can be completed in 10 minutes.

- **Memory: (screening, cycles 6, 12, 18 and 24):** (Appendix 31): This 7 question assessment (all YES/NO responses) will be used to assess memory and can be completed in 2 minutes.

- **Falls:** (Appendix 31) Of interest in the proposed study are the # of falls, the # of injurious falls, and medical care resulting from a fall. A fall is defined as unintentionally coming to rest on the ground or at some other lower level, not as a result of a major intrinsic event (e.g., stroke or syncope) or overwhelming hazard. An "injurious" fall is one that results in fractures, head injuries, sprains, bruises, scrapes, or serious joint injuries, or where the participant seeks medical care. These questions can be answered in a few minutes.

- **Dietary intake** (Appendix 6) **(screening, cycles 12, and 24)** will be assessed using a country-specific food frequency questionnaire (FFQ). Participants will complete this at the three time-points using a standardised FFQ. The FFQ can be completed in 45-60 minutes.

- **Exercise Motivation: (screening, cycles 6, 12, 18 and 24)** (Appendix 33)**:** This 9 question assessment asks the participant to rate how they feel about exercising regularly and can be completed in 3 minutes.

- **Cost of Participation (cycles 6 and 12, administer after on-site visit)** (Appendix 34-SE and Appendix 34-SDE)**:** This short survey will assess the following 4 parameters: Study contact frequency, health service usage; time investment; out-of-pocket expenses associated with participation in the study over the past cycle.

5.5 Study Assessments by Visit

5.5.1 Screening (within 28 days of CPET exercise assessment visit)

5.5.1.1 Review the study with the patient (and patient's legal representative, if applicable) and obtain written informed consent

5.5.1.2 Assign a Screening ID and enter the patient in the online Screening database

5.5.1.3 Collect the patient's demographic data and medical history,

including history of prostate cancer, diagnosis date, tumour histology, prior and current treatments, current sites of metastasis, last three PSA values and their corresponding dates, and other eligibility information (e.g. patient questionnaires, ECOG)

5.5.1.4 Confirm medical history eligibility with site PI

5.5.1.5 Obtain physician clearance

5.5.1.6 Record concomitant medications in database to be confirmed with patient at the exercise assessment visit

5.5.1.7 Request Halabi variables: PSA, LDH, albumin, haemoglobin, alkaline phosphatase

5.5.1.8 Set up screening CPET exercise assessment visit (only once all other eligibility criteria are met)

5.5.1.8.1 Review concomitant medications and adverse events with patient *(recorded from time of signed informed consent)* (SOM: Appendix 11 and 12)

5.5.1.8.2 Collect resting measures - electrocardiogram, vitals, etc.

5.5.1.8.3 Record anthropomorphic measurements (height, weight, waist/hip circumferences)

5.5.1.8.4 Complete CPET. The following data must be recorded: relative and absolute VO_2max, ventilatory threshold, maximum heart rate, respiratory quotient (SOM: Appendix 13). CPET must be completed within 14 days of Cycle 0, Day 1, which is the day when the final baseline exercise assessments are performed in both arms, and is also the first day of training in the intervention arm.

5.5.1.8.5 If patient successfully completes all eligibility criteria (including questionnaires, FFQ, CPET, etc.) the SCC should be notified via the Enrolment Worksheet. If SCC gives approval, patient should be randomised within the study database. The patient will be randomised to intervention or control. Baseline (Cycle 0, Day 1) must occur within 14 days of CPET.

5.5.1.9 If available, request archival FFPE tumour blocks or tumour slides from consenting patients for biomarker analysis

5.5.2 Baseline Cycle 0 Day 1 – Exercise Assessment Visit

5.5.2.1 Record date of visit

5.5.2.2 Collect blood and urine for research

5.5.2.3 Request fasting lipid profile (LDL, HDL, Triglycerides), fasting glucose, HbA1c

5.5.2.4 Record resting measures including resting blood pressure, resting heart rate and SpO2.

5.5.2.5 Discuss any adverse events since Screening; and record any

bone pain (VAS) or fatigue (VAS).

5.5.2.6 Perform 400m walk test

5.5.2.7 Complete 1 repetition maximum (RM) testing; chest press, leg press, seated row, and leg extension

5.5.2.8 Complete Constant Load Exercise Test (intervention arm)

5.5.3 Within 7 days on or after Day 1 of Cycles 6, 12, 24 – ARMS A & B

Study Blood Draw Visit

5.5.3.1 Collect research fasting blood (cycles 6, 12, 24) and urine (cycles 6, 12, 24)

5.5.3.2 Request fasting lipid profile (LDL, HDL, Triglycerides), fasting glucose, HbA1c (cycle 6)

5.5.3.3 Request Halabi variables: PSA, LDH, albumin, haemoglobin, alkaline phosphatase (cycle 6 and 12)

5.5.4 Within 7 days on or after Day 1 of Cycles 6, 12, 18, 24 – Exercise Assessments, ARMS A & B (to be completed on two days at least 48 hours apart at Cycles 6 and 12. Only "Day 2" tests are required for Cycles 18 and 24).

5.5.4.1 Record date of assessment

5.5.4.2 Confirm completion of questionnaires

5.5.4.3 Record any adverse events and changes to concomitant medications. Record bone pain (VAS) and fatigue (VAS).

5.5.4.4 Record resting measures including resting blood pressure, resting heart rate and SpO2, ECOG

5.5.4.5 Perform cardiopulmonary exercise test with ECG (Day 1 of cycle 6 and 12 only)

5.5.4.6 Perform 400m walk test (Day 2)

5.5.4.7 Perform 1RM strength assessment chest press, leg press, seated row, and leg extension (Day 2)

5.5.4.8 Complete Constant Load Exercise Test (Day 2).

NOTE: Please see Table 1, footnote 14 for adverse events collection & reporting, and Table 1, footnote 15 for medication collection & reporting.

5.5.5. Cycle 0 (within 7 days on or after Day 1) – One to three Exercise Training Visits per 7 days for ARM A

Exercise session (1 to 3 supervised exercise sessions per 7 days – refer to Section 6.1 for details)

- **Day 1**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure, and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High load, low volume resistance training; high-intensity interval aerobic training.
  - **Outcomes:**
    - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure

- **Cool down:** Trunk flexion and extension exercises and static stretching

- **Day 2**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High intensity continuous aerobic training
  - **Outcomes:**
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

- **Day 3**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** Moderate load and volume resistance training; high-intensity interval aerobic training
  - **Outcomes:**
    - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

5.5.6 Every 7 Days for 8 cycles starting from Cycle 1 (within 7 days on or after Day 1) – One to two Exercise Training Visits and One Self-Managed Exercise Session per 7 Days for ARM A

Exercise session (2 supervised sessions and 1 self-managed session per 7 days)

- **Day 1 (Supervised)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High load, low volume resistance training; high-intensity interval aerobic training.
  - **Outcomes:**
    - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

- **Day 2 (Self-Managed)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High intensity continuous aerobic training.
  - **Outcomes:**
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

- **Day 3 (Supervised)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** Moderate load and volume resistance training; high-intensity interval aerobic training

- **Outcomes:**
  - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
  - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
  - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure

Cool down: Trunk flexion and extension exercises and static stretching

5.5.7 Every 7 Days for 3 cycles starting from Cycle 9 (within 7 days on or after Day 1) – One Exercise Training Visit and Two Self-Managed Exercise Sessions per 7 Days for ARM A

Exercise session (one supervised session and two self-managed sessions per 7 days):

- **Day 1 (Supervised)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5-10 minutes cycling at a light to moderate intensity
  - **Exercise:** High load, low volume resistance training; high-intensity interval aerobic training.
  - **Outcomes:**
    - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure

  Cool down: Trunk flexion and extension exercises and static stretching

- **Day 2 (Self-Managed)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High intensity continuous aerobic training.
  - **Outcomes:**
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

- **Day 3 (Self-Managed)**
  - **Assessment:** Bone pain (VAS), Fatigue (VAS), resting heart rate, resting blood pressure and record any new adverse events or changes to medication.
  - **Warm up:** 5 minutes cycling at a light to moderate intensity
  - **Exercise:** High load, low volume resistance training; high-intensity interval aerobic training.
  - **Outcomes:**
    - Resistance Exercise: Number of sets, number of repetitions, weight lifted.
    - Aerobic Exercise: Work interval, rest interval, number of repetitions, RPE achieved.
    - Sessional Data: Sessional RPE, post-aerobic heart rate, post-session blood pressure
  - **Cool down:** Trunk flexion and extension exercises and static stretching

5.5.8 Day 1 of Cycles 0-23 (within 7 days on or after Day 1) – Exercise Testing in ARM A

5.5.8.1 Record date of assessment

5.5.8.2 Perform constant load exercise test

5.5.8.3 Complete 1RM testing; chest press, leg press, seated row, and leg extension (Cycles 0, 6, 9, 12 and 18)

5.5.9 Every 6 cycles (Cycle 6, 12, 18, and 24) within 7 days of Day 1

Medical clearance(s)* must be obtained from the patient's treating physician **prior** to exercise testing and/or training on Day 1 in the absence of any SAEs (SOM: Appendix 9).
* For any patient under that management of a cardiologist, additional clearance by his cardiologist is necessary at Cycles 0, 6, and 12.

5.5.10 Cycle 24/ Off-Study visit (within 7 days on or after Day 1) ARMS A & B

- Collect updated medical history
- Record ECOG PS, vital signs, patient weight, waist, and hip circumference
- Note concomitant medications (including WHO analgesic scale) and adverse events
- Assess disease progression from baseline
- Record any symptomatic-skeletal events
- 1-RM testing
- 400 m walk test
- Constant Load Exercise Test (Arm A only)
- Collect Research Blood and Urine
- BPI-SF, FACT-G, EPIC-26, FACIT-Fatigue, EQ5D, EORTC QLQ-30, STAI, CES-D (if not completed within 42 days – half the time between questionnaire assessments)
- Modified Godin, other exercise, and memory questionnaire (if not completed within 84 days - half the time between questionnaire assessments)
- FFQ (doesn't follow the 84-day stipulation)

5.5.11 Safety Follow-up (28 Days following Day 1 Cycle 24) ARMS A & B

5.5.11.1 Record any adverse events

5.5.11.2 Record any changes to concomitant medications

5.5.12 Post-Study Survival Follow-Up ARMS A & B (questionnaires and WHO analgesic scale once yearly; survival, disease progression, SSE twice yearly)

- Survival status
- Disease progression
- Symptomatic-skeletal event
- WHO analgesic scale
- A subset of the following questionnaires will be used:
- BPI-SF, FACT-G, EPIC-26, FACIT-Fatigue, EQ5D, EORTC QLQ-30, STAI, CES-D, memory
- Modified Godin and other exercise questionnaire

6 ARM A: EXERCISE INTERVENTION (SOM: Appendix 14)

6.1 Supervised Exercise Plan (Cycles 0-11)

The exercise intervention will include 48 weeks of aerobic and resistance training three times per week with the goal of delivering three moderate-to-vigorous aerobic training sessions and two structured resistance training sessions each week. A total of 88 supervised sessions should be completed within Year 1, in the event that the patient does not have any AEs that would prohibit him from reducing the number of exercise sessions. As long as the prescribed supervised dose is 88 sessions in Year 1, there is flexibility regarding the number of supervised sessions in a given week in Year 1.

Original Program: We strongly advise patients to adhere to the original program, with patients receiving three supervised exercise sessions in weeks 1-4 (Cycle 0), prior to the supervised exercise sessions tapering

throughout the program to two supervised sessions and one self-managed session for weeks 5-36 (Cycles 1-8) and one supervised training session and two self-managed sessions for weeks 37-48 (Cycles 9-11).

Flexible Entry: Although patients randomised to Supervised Exercise are **requested** to complete 3 supervised exercise sessions per week during Cycle 0 (totalling 12 supervised exercise sessions in this cycle), we recognise that some patients may require an 'easier' entry into the study in order to agree to enrol. This **flexible entry** option is permitted, where patients may complete a minimum of 1 to a maximum of 3 supervised sessions each week in Cycle 0, prior to joining the 'full program' from Cycle 1 onwards. However, while we allow the flexibility of less than 3 supervised sessions per week, those sessions will need to be made up later in Year 1 such that they complete the 88 sessions within Year 1. If using a flexible entry option, please prioritise the combined high-intensity interval training and resistance training sessions (Day 1 or Day 3 above) as it is easier to insert moderate-intensity continuous training sessions (Day 2) later in the program, when recovering missed supervised sessions. Examples of flexible entry plans are included in the SOM.

Exercise prescription will be tailored to the participant's baseline cardiopulmonary and strength assessments, and baseline conditions. The three training sessions each week will be **generally** structured as follows, with subtle alterations for variety, periodisation **and autoregulation**:

Day 1 - High load, low-volume resistance training and vigorous, high intensity interval aerobic

Day 2 - Moderate intensity continuous aerobic training

Day 3 - Moderate load and volume resistance training and vigorous, high intensity interval aerobic training

Exercise training will take the form of a periodised program. Training will be periodised within cycles of both 7 days (microcycle) and 28 days (mesocycle) duration. A periodised training approach allows training to be systematically organised into training phases to maximise the stimulus to physiological adaptation while reducing risk of injury, overtraining and staleness.

Within each week, Day1 training will involve high load and low volume resistance training in addition to high intensity interval aerobic training, the second day will consist purely of continuous aerobic training, and the third day will be moderate load and moderate volume resistance training and high intensity interval aerobic training. To achieve periodisation across the mesocycle, intensity of both aerobic and resistance training will increase with matching decreases in volume. On the first training day of each cycle the intensity will be dropped, volume increased and the pattern repeated across the cycle. For example, within each mesocycle training weight will progress linearly during the first 14 days, exercise volume will drop during days 15-21 and the cycle will finish with an unloading period from day 22-28.

6.1.1 Resistance Training

Resistance training exercises will be individually prescribed based on 1RM chest press, leg press and seated row assessments. Resistance training will consist of 2 to 4 sets at a load between 5 and 12 RM. For example, an 8RM is the weight that can be lifted only eight times. For non-athletes, there is little additional benefit performing resistance training sets to failure, so participants will be encouraged to finish the set one or two repetitions before neuromuscular failure.

During cycle 1 resistance exercise volume will be introduced incrementally, starting with 1 x 8RM. During subsequent cycles resistance training prescription will follow a standard linear progression as outlined in the SOM: Appendix 14. Participants will complete a total of two resistance training classes per week with a minimum of 48 hours recovery between resistance training sessions. The first session (Day 1) will comprise high load, low volume exercise where the load will vary from 5RM to 8RM. The second session (Day3) will comprise moderate load, moderate volume exercise where the load will vary from 10RM to 12RM. Exercises will comprise both lower body and upper body exercises. Exercise prescription will be modified based on the site and severity of the metastases. A sample of resistance exercises that could be completed include:

Lower Body	Upper Body
Leg press	Chest Press
Leg Curl	Seated Row
Leg Extension	Lat Pulldown
Lunges	Shoulder Press

6.1.2 Aerobic Training

Aerobic exercise prescription will be prescribed and modified based on autoregulation. The Constant Load Exercise Test will be completed within 7 days on or after Day 1 of Cycles 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11. Aerobic exercise prescription will take the form of high intensity interval training (HIIT) and continuous exercise.

HIIT involves alternating periods of work and active rest usually (but not always) on a ratio of 1:1 with work intervals of anywhere between 20 seconds and 4 minutes. This form of exercise prescription is designed to minimise the duration of exercise sessions by focusing on short bouts of high intensity aerobic. Such exercise has been demonstrated to be safe and highly effective in a range of patient populations including those with established cardiovascular disease and advanced metabolic syndrome[47] and may be more appropriate for advanced cancer patients who experience fatigue and discomfort with extended periods of long duration, low intensity aerobic exercise. HIIT sessions will be completed on Day 1 and Day 3 of each week following completion of prescribed resistance exercises. HIIT sessions will last for 20 minutes with a target intensity of ≥85%HRmax. Continuous vigorous aerobic exercise will be completed on Day 2 of each week for 35 minutes at an aerobic intensity of 60-85% HRmax.

Aerobic exercise training can be completed on a variety of exercise equipment including treadmill, cycle ergometer, cross trainer, rowing ergometer and arm crank ergometer. Decisions regarding individual exercise prescription will be made based on the site and severity the metastases.

6.1.3 Modifications to Exercise Prescription

The exercise physiologist /therapist leading the program may make amendments to the training protocol on an individual basis based on **autoregulation of training** and the site of the metastasis.

Autoregulation of training will be applied to enhance adherence and tolerance to the prescribed protocol. Using this method, the participant, in conjunction with their exercise trainer has the potential to adjust intensity and volume of the session according to their perceived capacity at that time. This is proving successful with other advanced cancer patients because it allows for auto-regulation of training load to account for fluctuations in fatigue state, changes in treatment phase, recovery capacity and scheduling commitments. For example, on a day when the participant feels highly fatigued they may elect to complete their resistance exercises as planned but postpone the aerobic exercise component to be done at home later in the week. The basis of auto-regulation training is that the participant achieves the target exercise mode, volume and intensity across any 1 or 3 cycles. Monitoring of autoregulation will be managed through review of the data on exercise volume completed, entered into the database by the exercise physiologist, trainer, etc. During the transition period participants will take responsibility for their own data entry at home, which will be provided to the exercise physiologist and added to our database. Participants will be provided with heart rate monitors to wear at home to monitor adherence to aerobic exercise prescription and from that record their average and maximum heart rate values, RPE, and exercise duration. Participants will record volume of resistance training completed through reporting number of sets, repetitions, and weight lifted.

Exercise prescription should also be modified in all participants based on the location and severity of bone metastases. A choice of exercises is available for both aerobic and resistance training. Decisions about appropriate exercise prescription should be taken by the exercise physiologist /therapist in consultation with the treating medical physician. Exercise selection should be modified where necessary throughout the program in response to participant feedback (i.e. tolerability, discomfort, bone pain, etc.). Any exercise which causes a participant issues should be removed from the program and replaced with one that is more appropriate and well tolerated.

Guidelines for exercise prescription based on site of metastases is provided in Table 3 below. All decisions must

be taken in consultation with the participant's treating medical physician and the ECC.

Table 3. Modification to Exercise Prescription by Site of Bone Metastases

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

√ = 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;
*** = exclusion of spine/flexion/extension/rotation;
WB = weight bearing (e.g. walking);
NWB = non-weight bearing (e.g. cycling);

6.1.4 Transition to self-managed exercise program

After 9 cycles, participants will be transitioned to self-management across a 3 cycle period. The number of supervised exercise classes will be tapered from 2 classes/week during cycles 1-8, to 1 supervised training session during cycles 9, 10 and 11. Aerobic exercise will be tapered first followed by resistance training classes. Throughout the supervised intervention period (Cycles 0-11), the intervention arm will complete the Constant Load Exercise test (within 7 days on or after Day 1 of Cycles 0-11) and 1RM strength testing (within 7 days on or after Day 1 of Cycle 9) to monitor progression and adherence to the prescribed protocol and inform continued progression of exercise prescription. Participants will be provided with heart rate monitors to wear for the duration of the supervised intervention (cycles 0-11) to monitor aerobic exercise prescription. The specifics of the self-managed program can be highly variable so long as across a given one to three cycle period the participant averages the equivalent of 75 minutes of vigorous aerobic exercise and two resistance training sessions each week. The key criteria for adherence and compliance will be that the participant meets the target aerobic and resistance training as per their individual exercise prescription. Participants will be reassessed within 7 days on or after Day 1, Cycle 12, following which they will be instructed to continue with self-managed exercise until Day 1, Cycle 24, disease progression, or patient mortality, whichever occurs first. The intervention period will cease at Cycle 24.

6.1.5 Missed sessions

Missed sessions should be rescheduled within the same week, if possible, while allowing at least 48 hours between resistance exercise sessions. Three sessions total (supervised and self-managed sessions) are recommended per week; however up to 3 sessions can be recovered (added) per week if missed in other weeks, totalling a maximum of 6 sessions within one week. The total number of supervised sessions and self-managed exercise sessions should remain the same as originally planned for in Year 1. When recovering missed sessions in a given week, we strongly advise to add 1 additional session per week (totalling 4 exercise sessions) where feasible, so as to not overwhelm the patient. Supervised sessions can occur during the week, which might require self-managed sessions to be moved to a mid-week and/or weekend day to facilitate recovering missed sessions. In the event that more than one missed session is being recovered in a given week, you may reduce volume/intensity in collaboration with the exercise coordination centre to prevent patient overreach. Incorporating additional exercises into a scheduled session to make up missed exercises is allowed and should be discussed with the ECC.

Exacerbation of symptoms such as fatigue should not result in missed sessions, as each training session can be adjusted (auto-regulated) to the patient's current condition on that day. Attendance will be defined as the number of in-person exercise sessions attended divided by the total number of planned supervised sessions. Exercise physiologists/trainers, leading the intervention will guide modification of the prescribed protocol based on the participant's capacity and perception of effort at the time of presentation to each exercise session in line with the principles of auto-regulated training outlined above. The number of missed sessions per participant and the reasons for missing sessions must be recorded and reported. If a participant misses an exercise session, they will be contacted by the research team to determine the reason and to reschedule the session. Every effort must be made by the research team to reschedule missed sessions or add extra exercise to current sessions in order to meet exercise targets.

Patients are permitted to take holidays however must commit to self-management of exercise during this period. During pre-planned or spontaneous holidays for patients (while on-trial), and/or due to unforeseen circumstances precluding attendance to a supervised session (such as an illness to spouse, or conflicting medical appointment), patients may complete a self-managed session under the strict guidance and overview of the site's research coordinator and exercise physiologist (to be recorded). If this occurs, a self-managed session replacing a supervised session in this way must be recorded in REDCap. If no session is performed to recover the missed session (without any adverse event, or other justifiable reason), this will be recorded in REDCap. During holidays, if patients do not have access to exercise facilities or equivalent items of use, these can be recovered during subsequent weeks within the Year it occurs (as is the definition of autoregulation; to ensure the overall program is upheld). This will be monitored by the Study and Exercise Coordination Centres during routine monitoring visits.

6.1.6 Trainer/Exercise Physiologists Training Program

Exercise professionals must complete an online training course (6 education modules and 3 protocol modules) on the protocol's exercise assessment and intervention methods. Trainers will view tutorials on the standard operating procedures, videos of specific tests/exercises, and guidelines on modifying assessments/exercises based on the patient's physical condition. A website with a discussion forum for trainers to submit queries and to discuss issues pertaining to the intervention will be maintained throughout the intervention period. This training program will include site requirements and ECC expectations in site monitoring of patients and ensuring regular and accurate entry into Physitrack.

6.1.7 Return to Exercise Training Following an Adverse Event

Return to exercise following reporting of an adverse event which requires updated physician clearance will be discussed on a case by case basis with the Exercise Coordinating Centre. Where physician clearance to return to exercise is deemed necessary, the participant will only be allowed to return to exercise training when physician clearance is provided in writing. The exercise physiologist/therapist supervising the exercise program will modify the program accordingly at re-introduction. A template form for physician approval for a patient to return to exercise is provided in SOM: Appendix 9. If no physician clearance is deemed necessary the participant can return to training upon clearance from the exercise physiologist/therapist.

6.1.8 Behavioural Support Program (Intervention Arm Only)

Participants will be asked to complete at least one unsupervised exercise session per week (hereafter referred to as self-managed exercise) starting in Week 5 (Cycle 1). The more self-managed exercise the participants are asked to engage in, the more behavioural support will be provided. The behavioural support will be provided utilizing text messages rooted in constructs/strategies from Social Cognitive Theory (SCT) and the Theory of Planned Behaviour (TPB). The overarching focus of the behavioural support will be to increase/enhance perceived control in task-specific exercises and overcoming individual barriers to exercise. The behavioural support provided will be encompassing, consistently delivered, and provided to each participant throughout the program. There will be four 'levels' of behavioural support (Table 4):

1. 3x/week supervised (cycle 0)

2. 1x/week self-managed; 2x/week supervised (cycles 1-8)
3. 2x/week self-managed; 1x/week supervised (cycles 9-11)
4. Totally self-managed; 1x/cycle supervised (cycles ≥ 12)

Table 4. Guidelines for Level of Behavioural Support

Level of Self-Management	Behavioural Support Components
No self-management 3x week supervised Cycles 0	The behavioural support will focus on: ○ Perceived competence ○ Identifying and overcoming barriers to exercise ○ Goal setting ○ Enhancing self-efficacy ➢ 1x per week pt. would get a text message/e-mail emphasising one of the topics above "signed" by the exercise specialist. Each week would be a different message working "down" off the list
1x week self-managed; 2x week supervised Cycles 1-8	The behavioural support will focus on: ○ Perceived independence ○ Securing social support ○ Maintaining/enhancing self-efficacy ○ Identifying and overcoming barriers to exercise ○ Self-monitoring ○ Goal setting ➢ 2x per week pt. would get a text message emphasising 2 of the topics above "signed" by the exercise specialist – each week would be a different pair working "down" off the list.
2x week self-managed; 1x week supervised Cycles 9-11	The behavioural support will focus on: ○ Identifying and overcoming barriers to exercise ○ Finding areas/ways/places to exercise ○ Self-monitoring ○ Goal setting ○ Time management ○ Lapsing/Relapsing/Collapsing ○ Gaining confidence ○ Perceived independence ○ Making exercise fun ○ Perceived competence ○ Staying motivated ○ Maintaining/enhancing self-efficacy ○ Securing social support ➢ 3x per week pt. would get a text message emphasising 2 of the topics above "signed" by the exercise specialist – each week would be a different pair working "down" off the list
Totally self-managed; 1x supervised session approximately every four weeks Cycles ≥12	The behavioural support will focus on a 'kitchen sink' approach: ○ Identifying and overcoming barriers to exercise ○ Finding areas/ways/places to exercise ○ Self-monitoring ○ Goal setting ○ Time management ○ Lapsing/Relapsing/Collapsing ○ Gaining confidence ○ Perceived independence ○ Making exercise fun ○ Perceived competence

- Staying motivated
- Maintaining/enhancing self-efficacy
- Securing social support

➢ 5x per week pt. would get a text message emphasising 2 of the topics above "signed" by the exercise specialist – each week would be a different pair working "down" off the list.

6.1.9 Training of Centres in the Behavioural Support Component

All research staff with potential direct contact with participants at any time point, including fitness assessments, exercise program prescription, exercise supervision, and phone or in-person contact, will complete a web based training (approximately 45-60 minutes) on behavioural support. The training includes an on-line exam that everyone must score at least 80% correct responses. The centres are responsible for ensuring that all personnel are trained and must keep records of training compliance. This training will need to be completed before any exercise testing or supervised exercise sessions start.

7.0 PSYCHO-SOCIAL SUPPORT (Supervised Exercise and Self-directed Exercise Groups)

Psycho-social support will be provided for all participants in the study. Participants will be provided with a two-or three-page newsletter each cycle either via e-mail or paper mail. The newsletters will include information on a variety of topics relevant to prostate cancer survivors. Participants will be sent one topic per cycle. Content for the psycho-social support newsletters will include:

Newsletter 1 "Staying Healthy – Lifestyle Behaviours"
Newsletter 2 "Goal Setting"
Newsletter 3 "Managing Fatigue"
Newsletter 4 "Bone Health"
Newsletter 5 "Side Effects of Treatment"
Newsletter 6 "Maintenance of Health Behaviors"
Newsletter 7 "Depression"
Newsletter 8 "Securing Social Support"
Newsletter 9 "Pain Management"
Newsletter 10 "Sexual Intimacy"
Newsletter 11 "Cognitive Changes"
Newsletter 12 "Gaining Control"
Newsletter 13 "INTERVAL: Your Participation"
Newsletter 14 "Hormone Therapy"
Newsletter 15 "Sweets and Sweeteners"
Newsletter 16 "Maintaining Control"
Newsletter 17 "Communication"
Newsletter 18 "Optimize your Sleep"
Newsletter 19 "Managing Stress"
Newsletter 20 "Nutrition & Fatigue"
Newsletter 21 "Plant-Based Diets"
Newsletter 22 "Cognitive Changes: Memory"
Newsletter 23 "Optimize Your Quality of Life"
Newsletter 24 "Beyond the INTERVAL Study"

8.0 METABOLIC RESEARCH STUDIES

8.1 Rationale

Understanding how exercise affects prostate cancer biology and clinical outcomes among men with prostate cancer requires in-depth interrogation of candidate biological systems and pathways. Several potential

mechanisms (outlined in Section 1.2) have been proposed to explain the effect of exercise on disease progression, the incidence and progression of comorbidities, treatment-related side effects, and overall survival among men with prostate cancer. Based on the prevalence of metabolic and endocrine dysfunction in men with MCRPC, the established benefit of high intensity aerobic and resistance exercise for metabolic health in various populations, and the highly-integrated regulation of inflammation, energy metabolism, and endocrine systems,[48] we propose to focus the initial metabolic research studies on three candidate pathways: systemic inflammation, insulin/glucose metabolism, and androgen biosynthesis.

8.2 Hypotheses

- Men randomised to exercise will have a smaller increase in systemic inflammation over time compared to men randomised to the control group, as measured by circulating IL1β, IL2, IL6, TNFα adiponectin, and C-reactive protein (CRP) levels.
- Men randomised to exercise will have improved insulin sensitivity over time as seen by lower circulating insulin levels and improved glucose tolerance compared to men randomised to the control group, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) and circulating levels of insulin, glucose, C-peptide, HbA1c, and IGF-1.
- Baseline levels of testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA), 17-hydroxyprogesterone, 17-hydroxypregnenolone and progesterone are affected by exercise
- High levels of systemic inflammation, insulin resistance, and low androgens at baseline and over time will be associated with shorter OS among men with mCRPC.
- Changes in inflammatory biomarkers, insulin/glucose metabolism, and androgens will mediate the hypothesized relation between exercise and OS among men with mCRPC.

8.3 Blood Collection for Metabolic Studies

Fasting Blood (26 ml) will be taken for the metabolic research analyses at baseline and Cycles 6, 12 and 24 from all consenting patients in both Arms A and B. Blood will be processed to plasma, buffy coat and serum. Fasting blood will be taken in the morning following an overnight fast of at least 12-hours where there was no food intake and a minimum of 48 hours since the last vigorous exercise session. The time of the blood draw and the last meal should be recorded. Blood draws can occur on the same day as the exercise assessment, prior to commencement of the assessments.

8.3.1 Plasma/Buffy Coat

20 ml of fasting blood will be collected in EDTA tubes and processed to plasma. Blood samples will be labelled with the patient's registration number and processed to plasma according to Research Blood Collection and Processing SOP (see SOM: Appendix 17) where the cellular components (buffy coat) will be retained after collection of the plasma. Aliquoted plasma and buffy coat will be stored at -80°C until batch transport. Blood needs to be processed within **one hour** of sampling.

8.3.2 Serum

6 ml of fasting blood will be collected in plain non-heparinised tubes and processed to serum. Blood samples will be labelled with the patient's ID number and processed to serum according to Research Blood Collection and Processing SOP (see SOM: Appendix 17). Serum will be collected in a manner which ensures suitability of the sample for downstream analysis of nucleic acids and protein factors. Aliquoted serum will be stored at -80°C until batch transport. Blood needs to be processed to serum within **2 hours** of sampling.

8.4 Biorepository

A secondary objective of the Metabolic Research Studies is to build a biorepository to enable future molecular and protein studies to thoroughly interrogate the effect of exercise among men with MCRPC at the systemic, muscular, and prostate-specific level. Serum, plasma and buffy coat will form part of this biorepository in addition to the samples discussed briefly below that will be collected from consenting patients.

8.4.1 Formalin Fixed Paraffin Embedded Tissue

Permission to access archived diagnostic, radical prostatectomy or bone marrow and metastatic biopsy formalin fixed paraffin embedded (FFPE) tissue blocks and slides will be requested from all patients in the consent form. The FFPE blocks will be collected at a later time point. Inability to access archived FFPE tissue will not exclude patients from participation in this study. All slides and blocks following cutting will be returned to their original pathology department.

8.4.2. Urine

Morning first void urine will be collected from all patients in the Arms A and B at baseline and within 7 days on or after Day 1 of Cycles 6, 12, and 24, and a minimum of 48 hours since the last vigorous exercise session. Patients will be provided with a sterile container by the research team. The patient will be asked to record the time of void. Urine will be processed according to Urine Collection and Processing SOP (SOM: Appendix 18). Urine will be collected in a manner which ensures suitability of the sample for downstream analysis of nucleic acids and protein factors. Aliquots will be stored at -80^{o}C.

8.5 Storage and Transport of Samples

- Plasma, serum, buffy coat and urine will be stored locally at sites at -80^{o}C until batch transport on dry ice to designated regional retention centres (SOM: Appendix 19)

8.6 Duration and retention of samples

All samples will be stored indefinitely at their final storage site as detailed in the SOM: Appendix 19. Access will be permitted only to individuals/groups who have received permission from the GAP4 steering committee. Investigators will request access to samples by petition to the GAP4 steering committee. Investigators will be required to provide specific hypotheses relevant to the goal of elucidating the role of exercise in prostate cancer patients and funding for any proposed biomarker assays.

9.0 OFF-TREATMENT

Subjects will remain on treatment until the Month 24 Off Study visit; however, a patient may be discontinued from study intervention at any time if the patient, the Investigator, or the DSMB feels that it is not in the patient's best interest to continue on study. If a patient must be discontinued, this will not result in automatic withdrawal of the patient from the study.

The following is a list of possible reasons for early discontinuation of study interventions:

- An adverse event that cannot be adequately managed with intervention modifications
- Protocol violation requiring discontinuation of study intervention
- Lost to follow-up
- Patient withdrawal of consent
- DSMB request for early termination of study
- Progression is NOT a reason for study termination

All patients discontinuing study interventions will complete an Off Study visit (if able), and enter into the follow-up period.

If a patient is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to contact the patient must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Subjects who withdraw will not be replaced.

Note: PROGRESSION: Every effort should be made to keep patients who progress on study for the duration of the trial period.

10.0 PRIMARY ENDPOINT CRITERIA FOR OVERALL SURVIVAL

Patients will be followed for death a minimum of 36 months after randomisation. Overall survival will be measured from the time of randomisation until death. Medical records and death certificates will be reviewed every 6 months to obtain survival status. Country-specific mortality status databases will also be searched annually; cause of death will be determined through review of medical and death records. Patients will be contacted once a year, and follow up with next of kin then alternate contact, if needed, if we do not hear from them.

11.0 SECONDARY ENDPOINTS

11.1 Disease progression

Data on disease progression will be obtained through review of patient medical records each cycle. Progression will be determined by the treating physician, and may include any of the following, based on PCWG-3 and RECIST 1.1 criteria:

- Bone scan: Appearance of ≥ 2 new lesions on bone scan, if bone scan >12 weeks after randomisation

- CT/MRI: ≥ 20% increase in the sum of diameters, taking the reference as the smallest sum on study. In addition to the relative increase by 20%, the sum must also demonstrate an absolute increase >5 mm. OR The appearance of one or more new lesions. OR Unequivocal progression of baseline unmeasurable lesions (see further details below). If the patient has measurable disease, there must be overall worsening in non-measurable disease such that the overall tumour burden has increased substantially. The designation of disease progression solely on the basis of change in non-measurable disease in the face of stable disease or partial response of the measurable disease is extremely rare.

- Development of an indication for initiating a therapy for MCRPC after randomisation, including, but not limited to, abiraterone, enzalutamide, chemotherapy, or radiation therapy.

- Symptomatic-skeletal related event (SSE).

Progression free survival will be measured from randomisation until the first of the following: first CT or bone scan documenting disease progression, initiation of a new therapy for MCRPC (clinical progression), or first occurrence of a SSE.

11.1.1 CT Scan Progression of Non-measurable Lesions

Progression will be defined based on PCWG;-3 and RECIST 1.1 as all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes 10-<15mm short axis) as well as truly non-measurable lesions. All non-measurable lesions should be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases, “unequivocal progression.” Multiple non-measurable lesions involving the same organ should be recorded as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

11.2 Symptomatic Skeletal Related Events

Time to first occurrence of SSE will be defined as the time from randomisation to documentation of any of the following (whichever occurs first) + 1 day:

- Use of external beam radiation therapy to relieve bone pain
- Occurrence of new symptomatic pathological bone fractures that may be vertebral or non-vertebral. Asymptomatic compression fractures detected by radiology review only will not be considered a SSE.
- Spinal cord compression
- Change in antineoplastic therapy to treat bone pain
- Surgical intervention to treat bone pain

Adverse event, concomitant medication, concomitant treatment, or survival follow-up CRFs and the participant’s medical record will be the source of these findings and presented as categorical data.

11.3 Analgesic/Opiate Use

Analgesic/opiate use will be assessed via BPI-SF, the WHO analgesic scale, and medical record review at entry

with a lead-in period (<28 days). The WHO analgesic scale will be completed every three cycles (based on medical review) and questionnaires will be administered every three cycles until month 24, and yearly thereafter.

11.4 Metabolic Biomarkers

Initial investigations will focus on analysis of biomarkers at selected time points; it is envisioned that additional funding will be acquired for investigation of additional time points.

Inflammatory and cytokine systemic milieu: Serum/plasma aliquots (baseline and cycle 6) from all Arm A and B patient samples are intended for interrogation of a panel of markers associated with inflammation including IL1β, IL-2, IL-6, TNFα and adiponectin. These samples may be run in single or multiplex reactions as appropriate using a commercial platform such as MesoScale Diagnostics. Results from these investigations will be correlated with c-reactive protein and measured outcomes of exercise response and disease progression.

Insulin/Glucose Metabolism: Serum aliquots (baseline and cycle 6) from all Arm A and B patient samples are intended for assessment of insulin levels by e.g. enzyme-linked immunosorbent assay (ELISA). Insulin sensitivity will be calculated using these fasting serum insulin values and plasma glucose determinations obtained in the additional clinical blood assessments, where the HOMA-IR method will be applied. C-peptide will also be assessed in all samples and used to monitor glucose levels longitudinally in both the intervention and control groups. Additional assays for IGF-1 will also be performed.

Androgen biosynthesis: Serum aliquots from all Arm A and B patient samples at baseline are intended for assessment of androgen levels (Testosterone, DHT, androstenedione, DHEA, 17-hydroxyprogesterone, 17-hydroxypregnenolone and progesterone) levels by mass spectrometry (MS). Previous studies using this assay have demonstrated results in a lower limit of quantitation of 1 pg per sample for testosterone and DHT, respectively. Intra-assay coefficients of variation generated using human serum for high-, mid-, and low-range samples were 3.5%, 3.1%, and 3.8% for testosterone and 6.3%, 4.3%, and 15.8% for DHT, respectively.

11.5 Physical Function

Physical function will be assessed using strength assessments (1RM), a cardiopulmonary exercise test (CPET) and a functional performance test (400m walk). Strength assessments will be quantified in kilograms lifted, and will be dependent upon the location and size of bone metastatic lesions present as to which tests are performed (Chest Press, Leg Press, Seated Row and Leg Extension). All strength assessments should be attempted if not contraindicated. Cardiopulmonary exercise capacity will be quantified by VO2peak (L.min and mL/(kg·min)) and workload achieved (watts) during a successful CPET (RPE ≥ 9). Functional performance will be represented by time (in seconds) taken to perform a 400m walk test.

11.6 Quality of Life

Symptoms will be considered independently of other outcome measures. Pain will be assessed via BPI-SF and medical record review at entry with a lead-in period (<28 days) and repeated measures will occur every three cycles. Changes occurring within 12 weeks of study initiation will be ignored in the absence of compelling evidence of disease progression. Response or progression of pain will be confirmed through repeat assessments separately by at least three weeks. Quality of life measured by the FACT-G, FACIT-Fatigue, QLQ-C30, EPIC-26, and EQ5D will be assessed every 3 cycles.

12.0 STATISTICAL CONSIDERATIONS

12.1 Endpoints

Our primary endpoint is OS. Secondary endpoints include PFS, pain, opiate use, cancer-related fatigue, symptomatic SSE, and QOL-adjusted OS. OS will be measured from the date of randomisation to date of death due to any cause.

12.2 Power and Sample Size for Primary Endpoint

This is a 1:1 randomised controlled trial in men with MCRPC. Registered and eligible participants will be

randomised with equal probability to one of two intervention regimens: supervised exercise for 12 cycles tapering to self-management for 12 cycles with psychosocial support or psychosocial support alone. We will stratify by whether the men are on active therapy or not at the time of registration (yes/no) and study site. A total of 866 men will enrol in this study to ensure at least 412 men evaluable for OS in each arm.

Null hypothesis (H_0)= There is no difference in OS between patients randomised to the exercise intervention plus psychosocial support vs psychosocial support alone.

Alternate hypothesis (H_A) = There is a difference in OS between patients randomised to the exercise intervention plus psychosocial support vs psychosocial support alone.

Considering a total enrolment period of 36-months and minimum 36 months follow-up for each patient after enrolment; assuming survival time follows an exponential distribution; and assuming a median OS survival of 33.5 months in the control arm, the sample size required to detect a hazard ratio (HR) of 0.78 with 80% power at significance level of 0.05 is 824, 412 men in each arm. Accounting for up to 5% of patients with missing data on OS, we aim to enrol 866 men. If we consider non-compliance of 10% in the intervention arm, which equates to 371 patients in the intervention arm who are compliant, this provides 77.7% power to detect an HR of 0.78, when comparing the 371 compliant patients with the 412 patients in the control arm at the significance level of 0.05.

12.3 Data Analysis

Demographic and baseline characteristics will be summarized across the stratification factors, within each arm and overall. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean (with standard deviation) and median (with range) will be used to describe symmetric and skewed continuous measurements, respectively.

12.4 Analysis of Primary Endpoint

The primary endpoint for the study is OS (defined in Section 10). An intent-to-treat approach will be used to analyse OS. Patients alive at the end of follow-up will be censored on the date of last contact (or, if no contact after the baseline visit, at the date of randomisation + 1 day). Kaplan-Meier methods will be used to estimate the median OS for each treatment arm as well as the 1-year, 2-year, and 3-year OS rates and corresponding 95% confidence intervals. A two-sided log-rank test, stratified by treatment status (on treatment Y/N) and study site, will be used to assess the effect of the intervention. Un-stratified log-rank tests will be examined as sensitivity analyses. Cox proportional-hazard regression models will be used to estimate the hazard ratio and its 95% confidence interval to quantify the effect of the intervention on OS, adjusting for stratification factor(s). First, the base model will be evaluated and then other potential confounding factors will be considered. We will also conduct secondary analyses with consideration for non-compliance and the number of supervised sessions completed.

12.5 Analysis of Secondary Endpoint: Progression-free Survival

PFS will be defined as the time from randomisation to the date of disease progression (defined in Section 11) + 1 day. Patients who have not progressed at the time of the analysis will be censored on the last date of contact OR death, whichever comes first. Patients with no data after randomisation will be censored on the day of randomisation + 1 day. An intent-to-treat approach will be used to analyse PFS. A two-sided log-rank test, stratified by treatment status at registration, will be used to assess the effect of the intervention. Kaplan-Meier methods will be used to estimate median PFS for each treatment arm and the 1-year, 2-year, and 3-year PFS rates and corresponding 95% confidence intervals. Cox proportional-hazard models will be used to assess the magnitude of the effect of the intervention, adjusting for stratification factors and other potential confounding factors.

12.6 Analysis of Secondary Endpoint: Symptomatic skeletal-related events (SSE)

Time to first occurrence of SSE will be defined as the time from randomisation to documentation of any of the following (whichever occurs first) + 1 day:

- Use of external beam radiation therapy to relieve bone pain
- Occurrence of new symptomatic pathological bone fractures that may be vertebral or non-vertebral. Asymptomatic compression fractures detected by radiology review only will not be considered a SSE.
- Spinal cord compression
- Change in antineoplastic therapy to treat bone pain
- Surgical intervention to treat bone pain

Adverse event, concomitant medication, concomitant treatment, or survival follow-up CRFs and the participant's medical record will be the source of these findings and presented as categorical data. Patients who do not experience a SSE will be censored on the date on which they were last known to be event-free. Patients with no data after randomisation will be censored at the date of randomisation + 1 day. The Kaplan-Meier method will be used to estimate the median time to SSE for each group and a log-rank test will be used to determine if there is a statistically significant difference in the time to SSE between the two groups. Cox-proportional hazard regression will be used to estimate the magnitude of the difference between groups and adjust for stratification factors and possible confounding factors.

12.7 Analysis of Secondary Endpoint: Pain

To assess pain severity (worst pain, least pain, average pain, current pain, pain interference with activities of daily living, and opiate use) between groups at 6, 12, 18, and 24 months, the two-sample Wilcoxon rank sum test and two-sample t test for continuous measurements will be used. To determine if progression of pain is different between the two groups over time, we will use generalised linear mixed models for repeated measures for each pain score with appropriate link function, where group, strata and covariates will be considered as fixed effects, and time will be considered as the repeated measure. We will also use area under the curve analyses, where appropriate. In order to complete this as an intention to treat analysis, patient with missing data due to failing health or death will be run multiple ways, including assigned scores of maximum pain and using last observation carried forward.

12.8 Analysis of Secondary Endpoint: Circulating Metabolic Biomarkers

Positively skewed variables will be log transformed prior to analyses. Graphical methods will be used in the first instance to show trends over time and differences between the intervention and control groups using box plots or line graphs. To test for differences between the intervention and control group, we will use two-sample *t*-tests with the assumption of unequal variance to compare baseline, 6, 12, and 24 month circulating inflammatory and energy metabolism biomarker levels, as well as mean changes and effect sizes in these measurements over the study period. Where differences are seen, these will be further investigated within the intervention group against compliance to exercise to demonstrate a dose response relationship. Biomarker assessment at baseline and 6 months are funded. Additional funding will be acquired for investigation of additional time points.

We will also calculate absolute changes in circulating inflammatory and energy metabolism biomarker levels, and use *t*-tests to test the null hypothesis that the average change in these measurements in the control and exercise groups is zero. We will use multivariate linear regression to examine the effect of the intervention on change in inflammatory and energy metabolism biomarker levels at 6, 12, and 24 months, adjusting for baseline levels. Additionally, to examine changes in metabolic biomarkers at various time points during the study period, we will utilise a mixed effects model with adjustment for baseline biomarker levels. Treatment assignment and time (6, 12, 24 months) and treatment × time interaction will be included as fixed effects. Biomarker assessment at baseline and 6 months are funded. Additional funding will be acquired for investigation of additional time points.

12.9 Analysis of Secondary Endpoint: Physical Function

To examine strength levels (kilograms lifted for chest press, leg press, seated row and leg extension), cardio-respiratory exercise capacity (oxygen consumption and workload achieved), and functional performance (time in seconds to complete 400m walk test) between groups at 0, 6, 12, 18 and 24 months when performed, the two-sample Wilcoxon rank sum test and two-sample t-test for continuous measurements will be used. To determine if changes in strength, cardiorespiratory exercise capacity and functional performance is different

between the two groups over time, we will use generalised linear mixed models for repeated measures, where group, strata and covariates will be considered as fixed effects, and time will be considered the repeated measure. In order to complete this as an intention to treat analysis, patients with missing data due to failing health or death will be run multiple ways, including assigned levels of physical function across metrics described, and using last observation carried forward.

12.10 Analysis of Secondary Endpoint: Quality of Life

To assess QOL scores (overall QOL, physical wellbeing, social/family wellbeing, emotional wellbeing, functional wellbeing, prostate specific concerns, fatigue, health status) between groups at 6, 12, 18, and 24 months, the two-sample Wilcoxon rank sum test and two-sample t test for continuous measurements will be used. To determine if the change in QOL is different between the two groups over time, we will use generalised linear mixed models for repeated measures for each QOL score with appropriate link function and group, strata and covariates considered as fixed effects, and time considered as the repeated measure. For the EQ5D analyses (QOL utility), we will compare area under the curve. We will consider one value set and country-specific value sets. In the absence of a country-specific value set, a set of values for a population that most closely approximates that country will be used. In order to complete this as an intention to treat analysis, patient with missing data due to failing health or death will be run multiple ways, including assigning scores of zero quality of life and using last observation carried forward.

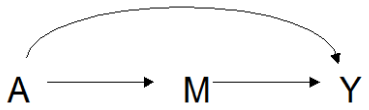
12.11 Other Secondary Analyses

12.11.1 Associations between Circulating Metabolic Biomarkers and OS

We will use multivariate Cox Proportional Hazards regression to examine whether circulating levels of inflammatory and energy metabolism biomarkers are associated with OS, adjusting for potential confounding factors and stratifying by intervention arm, treatment status at registration, and study site. Patients alive at the end of follow-up will be censored on the date of last contact (or, if no contact after the baseline visit, at the date of randomisation + 1 day). We will examine baseline levels as well as update levels over time using assessments at cycles 6, 12, and 24. The biomarkers will be modelled categorically and continuously, as appropriate. Biomarker assessment at baseline and 6 months are funded. Additional funding will be acquired for investigation of additional time points.

12.11.2 Analyses to Explore whether Metabolic Markers Mediate Hypothesized Relation between Exercise and OS

We will explore to what extent the hypothesized benefits in cancer-specific mortality in the exercise group are mediated by changes in inflammatory, energy metabolism, or androgen biomarker levels using a mediation analysis as developed by Vanderweele et al.[49,50] The mediation analysis will allow us to estimate the proportion of the effect of the exercise intervention on prostate cancer mortality (Y) that is mediated through the biomarkers of interest (A→ M →Y), and how much is explained by other causal pathways (A → Y) (see graphic below).



A is the exposure (exercise group)
M is the mediator (e.g. insulin, IGF, T)
Y is the outcome (mortality)

The causal direct and indirect effect measures can be calculated using Cox proportional hazards regression. The statistical analysis can be implemented using a publically-available SAS macro; moreover, it allows us to estimate these effects even if exercise and the biomarker levels interact.

12.11.3 Per Protocol Analyses

Secondarily, we will conduct analyses using a per-protocol analysis to investigate the possibility of a dose

response or threshold effect. Participants who attend 80% or more of the supervised exercise sessions will be considered to have complied with the protocol.

12.12 Interim Analyses

We are planning a feasibility study and three interim analyses: one for effectiveness, one for efficacy, and one for accrual. All interim data will be reviewed by the GAP4 steering committee and Data Monitoring Committee.

Feasibility study

The conduct of the study is dependent on patient willingness to participate in the study and compliance with the assigned intervention strategy, as well as the site's ability to provide the recommended intervention. We will start the trial at 1 site in advance of the GAP4 kick-off meeting (slated for early December 2015/early January 2016), and summarise challenges, lessons learned, and study updates from this pilot phase at the kick-off meeting.

Analysis 1: Effectiveness of the intervention

This futility analysis will determine whether the intervention has an effect on exercise parameters related to fitness and physical function, specifically measured by leg extensions and the 400m walk test. A change in these measurements between study arms will be based on the first 15% of patients (N=130) completing the first 6 months of the intervention phase. Data provided by Dr Rob Newton on observed group differences at 3 months in the first few patients in a similar trial, showed leg extensions to be improved by 6.26kg (average standard deviation (SD) 5.16, and 400m walk by 12.5 seconds, average SD 8.75, which represents effect sizes of 1.21 and 1.43, respectively. Unfortunately, due to small sample size, the confidence intervals around these effect sizes are quite wide.

	mean diff	SD (approx.)	estimated effect size	95% confidence interval
400m Walk	-12.52	8.75	1.43	(-0.48, -2.39)
Leg Extension	6.26	5.16	1.21	(0.33, 1.95)

We will complete this interim analysis when the first 130 patients complete 1RM and 400m walk testing on or within 7 days *after* Cycle 6, Day 1 (6 months after Day 1 of the intervention), and estimate the mean difference between the groups for both the 400m walk and leg extensions. Dr Newton's data is pilot data based on small sample sizes, so we have attenuated the expected effect size for these two parameters to 0.40; however, we will revisit the comparison when a larger dataset is available. We will consider an analysis similar in scope to this example: Assuming that the standard deviation of change in 400m walk is 8.75 and leg extension is 5.16 (based on preliminary data above), if the difference in leg extension strength between the two arms is less than 2.06kg *or* the difference in the 400m walk between the two arms is less than 3.5 seconds we will consider modifications to the protocol.

Analysis 2: Efficacy and possible early termination due to unequivocal results

The interim analysis plans to investigate the primary outcome when half of the required number of events for final analysis of overall survival (i.e., 315 events) will be carried out with $\alpha=0.0005$. A stringent alpha level has been chosen to reduce the amount of alpha spending prior to the final analysis with the full sample. The interim analyses will spend 0.001 of the 0.05 alpha requiring us to reach 0.05-0.001 = 0.049 for the final trial results to be considered statistically significant with an overall $\alpha=0.05$.

The interim analysis will be carried out to assess whether the study should terminate early due to an unequivocal result at the 0.0005 level. This interim analysis can result in recommendations that include modifications to the study, including termination of accrual, modifications to data collection, or early reporting of results. Recommendations will be made to the Steering Committee, who will make the final decisions.

The interim analysis will describe the limits of the effect size seen between the two arms of the study on overall survival. The limits will be calculated using a Cox proportional hazards regression model and use a two sided (1-0.001) = 99.9% confidence interval. If this confidence interval excludes a 22% or higher reduction in mortality or excludes 1 (no difference between the groups) the trial will already show a statistically significant finding with p<0.001. If the confidence interval does not contain a 22% increase in survival it is unlikely that exercise improves survival sufficiently to warrant the continuation of the study. Or if the confidence interval does not contain 1 it may be considered unethical to continue to randomise patients to the control arm. If this is the case, the results will be reported to the Steering Committee with a Kaplan Meyer plot to illustrate these findings, and the Steering Committee will make the final decision.

Analysis 3: Accrual assessment

The Steering Committee and Data Monitoring Committee will receive notification every 3 months of the interim and total accrual. We will request that all sites keep monthly accrual data to ensure complete data for this assessment. This would include number of patients who were invited to participate, interested, completed exercise screening days, and enrolled. The Steering Committee and Research Advisory Committee will make final decisions about expanding eligibility criteria, exploring alternative options, etc.

12.13 Additional Analyses

12.13.1 Health Economic Evaluation

An economic evaluation will be performed in parallel to the trial in order to assess the health benefits, additional costs, and potential savings of including exercise therapy as standard of care for men with mCRPC.
The cost analysis will follow international accepted guidelines for undertaking economic evaluation. Thus, the cost analysis will adopt a three-step process involving the identification, measurement, and valuation of the resource use (costs) associated with the delivery of the intervention, compared to the control group. Clinical data will be supplemented with patient and site information to measure the use of highly relevant clinical services and resources. Costs will be valued using appropriate country costs and will be converted into International dollars using purchasing power parity estimates.

13.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS

Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and coded. Adverse events shall be assessed at every cycle and the following details recorded on the CRF: type, severity, relationship to exercise intervention and disease, expectedness, SAE (yes/no), timing, action taken (if any) and outcome.

13.1 Definitions

13.1.1 Clinical Adverse Events (AE)

A clinical adverse event is any unfavourable or unintended sign, symptom, or disease temporally associated with the study intervention and occurring in a patient assigned to the intervention. All AEs reported from the date of informed consent until 28 days after the Off-Study visit will be considered. AEs are assessed by the exercise physiologist, trainer, etc. at on-site exercise visits and in all subjects (in person or by phone) on a monthly basis. This includes adverse clinical or laboratory findings, illness, or an exacerbation or progression of a disease/condition present at baseline. A list of standard questions will be used to assess any AEs, provided in the SOM.

In this trial, the study intervention is defined as supervised aerobic and resistance exercise. All potential participants will be screened via their medical charts as well as through in-person assessments to assess cardiovascular contraindications to exercise. Our multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated.

However, rare but serious AEs are possible. Those that may occur during either cardiopulmonary exercise testing (CPET) or exercise training include myocardial infarction (heart attack), stroke, unconsciousness or other serious injury.

- Events during a CPET are rare (<1/100,000 in well individuals and 1/10,000 in sick individuals). A trained health professional (e.g. medical staff and exercise physiologist) will monitor the exercise test in a location staffed by physicians, in the rare event that such an event occurs.
- Similar to a CPET, exercise training may cause temporary risks of an adverse cardiovascular event, such as a heart attack. The CPET with ECG-monitoring that must be completed prior to randomisation will ensure that all randomised participants are healthy enough to engage in exercise training.

Absolute and relative indications for stopping exercise (both testing and training) are provided in Table 5. In the event of a participant presenting with any of the below symptoms exercise should be stopped.

Table 5. Indicators for Stopping Exercise

Absolute indications for Stopping Exercise:

- Suspicion of a myocardial infarction or acute myocardial infarction (heart attack)
- Onset of moderate-to-severe angina (chest pain)
- Drop in systolic blood pressure (SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms
    - Hypotensive response resulting in SBP <60mmHg
- Signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin
- Severe or unusual shortness of breath
- CNS (central nervous system symptoms
    - Ataxia (failure of muscular coordination)
    - Vertigo (an illusion of dizzying movement)
    - Visual or gait (pattern of walking or running) problems
    - Confusion
- Patient's request to stop
- Irregular pulse
- Extreme fatigue
- Skeletal fracture
- Increased bone pain

Relative Indications:

- Increasing chest pain
- Physical or verbal manifestations of shortness of breath or severe fatigue
- Wheezing
- Leg cramps or intermittent claudication (grade 3 on a 4-point scale)
- Hypertensive response

Other examples of AEs include but are not limited to:

- Abnormal test findings (see specific criteria for AE reporting, below)
- Clinically significant signs and symptoms
- Changes in physical examination findings

- Worsening of signs and symptoms of the malignancy under study. Disease progression assessed by measurement of malignant lesions on radiographs or other methods **should not** be reported as an adverse event, unless the outcome is fatal during the study or within the safety reporting period (up to 28 days after the 24th cycle) – see definition of serious adverse event below.
- Signs or symptoms resulting from exercise overload
- Drug interactions

For laboratory abnormalities, the criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from study, significant additional concomitant treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the Investigator

13.1.2 Serious Adverse Events (SAE)

A serious adverse event (SAE) is any adverse event occurring at any level of intervention that results in any of the following outcomes:

- Results in death. *If the malignancy under study has a fatal outcome during the study or within the safety reporting period, the event leading to death should be reported as a Grade 5 SAE; death is an outcome and not the adverse event in itself.*
- Is life-threatening (i.e., immediate risk of death from the reaction as it occurred). *It does **not** include a reaction which hypothetically might have caused death had it occurred in a more severe form.*
- Requires or prolongs inpatient hospitalisation (i.e., the event required at least a 24-hour hospitalisation or prolonged a hospitalisation beyond the expected length of stay). Hospitalisation admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier)
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardise the participant and require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalisations for:

- Routine treatment or monitoring of the studied indication, not associated with deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care or social admissions

13.1.3 Non-Serious Adverse Events

All other events.

13.2 Expectedness

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed above or included in the following list:

Bone pain, pathological skeletal fracture
Musculoskeletal injury (sprain, strain)
Joint pain
Falls
Muscle soreness

13.3 Attribution

A suspected adverse reaction means any adverse event for which there is reasonable possibility that the intervention caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the intervention and the adverse event.

The Investigator will assign attribution of the possible association of the event with the study intervention using the following definitions:

Unrelated to the exercise intervention: The adverse event is *Unlikely* or *Not Related* to the exercise intervention

Related to exercise intervention: The adverse event is *Possibly*, *Probably*, or *Definitely* related to the exercise intervention.

13.4 Severity

Signs or symptoms should be graded and recorded by the Investigator according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (SOM: Appendix 30). When specific adverse events are not listed in the CTCAE, they are to be graded as mild, moderate, severe, or life-threatening according to the following grades and definitions:

Table 6. AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age- appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

13.5 Reporting Requirements

All AEs and SAEs whether reported by the patient, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means must be recorded in the patient's medical record and on the AE form in the online study database. All AEs should be reviewed by the site PI. The Investigator is responsible for notifying the Institutional Review Board/ Independent Ethics Committee (IRB/IEC) about AEs in accordance with local regulations.

13.5.1 SAE Reporting

At screening, the reporting period for SAEs begins from the time the patient provides informed consent and prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure through and including 28 days after the Off-Study visit. All SAEs occurring during the study must be reported to the site PI by study-site personnel within 24 hours of their knowledge of the event. This timeframe also applies to additional new information (follow-up). SAEs will be reported via a study supplied SAE form and sent to the SCC, to be reviewed by the data safety and monitoring committee, within 24 hours of site PI awareness. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study will be provided as a separate document. The Investigator is also responsible for notifying the Institutional Review Board/ Independent Ethics Committee (IRB/IEC) in accordance with local regulations. All events should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first.

13.5.2 Reporting Deaths

Regardless of relationship to the exercise intervention, all deaths on study should be reported through and including 28 days after the end of the Off-Study visit. Deaths occurring after this period do not have to be reported as SAEs unless considered related to the exercise intervention. For all SAEs, the Investigator is obligated to pursue and provide information to the SCC in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Study Coordination Centre.

13.5.3 Non-Serious AE Reporting

Non-serious adverse events should be recorded on the AE CRF (SOM: Appendix 12) from the time of informed consent until 28 days after cycle 24. All events should be followed to their resolution, until the Investigator assesses them as stable, irreversible, or until the patient is lost to follow-up, whichever comes first.

13.6 AE Monitoring

The Data Safety and Monitoring Committee will convene on a quarterly basis, and additionally at the discretion of the Steering Committee, throughout the study period to review safety procedures, protocols, and specific cases.

13.7 Statistical Analysis of Adverse Events

Adverse event rates will be summarised with frequency and percentage within each arm and across arms. Rates between groups will be compared using the intention-to-treat approach. In addition, AE incidence rates will be summarised by severity and relationship to the intervention. Intervention-related AEs are those judged by the Investigator to be at least possibly related to the intervention. Adverse events with missing severity or relationship to the intervention will be classified as severe and treatment-related, respectively. Patients with multiple occurrences of events will only be counted once at the maximum severity for each preferred term, SOC, and overall. Deaths that occur within 28 days after the 24th cycle clinic visit are defined as on-study deaths.

13.8 Return to Exercise Training Following an Adverse Event

This is detailed in Section 6.1.7.

14.0 PROTOCOL VIOLATION AND WITHDRAWAL OF PARTICIPANTS

14.1 Protocol violation

A protocol violation occurs when a patient or Investigator fails to adhere to specific protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria. Protocol violations for this study

include, but are not limited to:

- Failure to meet the inclusion/exclusion criteria
- Failure to complete the exercise intervention as stated within the protocol
- Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The central ECC and central SCC, in consultation with the Site PI, will determine if a protocol violation should result in withdrawal of a patient.

14.2 Withdrawal of participants

Participants are free to withdraw from the trial at any stage without providing a reason and without consequence. This information will be stated in the participant information leaflet. Participants can inform the research team at their local site of their decision to withdraw. If a participant withdraws from the study, any data collected on him up to that point in the study will go forward for study analysis. This information will be stated in the participant information leaflet. If a participant withdraws from the intervention, but provides consent to complete subsequent follow-up measurements he will continue to attend study assessments and data will be used for intention-to-treat analysis. If a patient chooses to withdraw prior to cycle 24, we will ask for an Off-Study research blood draw if research bloods were not taken within the last 56 days. Reasons for stopping the intervention will be recorded and reported.

Reason	Comment
Self-withdrawal (withdrawal of consent)	Patients may permanently discontinue study treatment and withdraw from the study anytime for any reason. Following study intervention discontinuation, patients will have protocol-required safety and long-term follow-up assessments unless the patient specifically declines further follow-up.
Adverse event or intercurrent illness	Any intolerable adverse event (associated or not associated with the study intervention) that cannot be ameliorated by the use of adequate medical intervention or that in the opinion of the site investigator would lead to undue risk if study treatment were continued.
Gross noncompliance with protocol (violation)	The investigator may request permanent discontinuation of study treatment in the event of a major protocol deviation, lack of cooperation, or complete noncompliance. Outcome and follow-up data will still be requested unless the participant specifically declines further follow-up.
Loss to follow up	Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete study-related assessments, and record outstanding data.

15.0 DATA MANAGEMENT AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each patient in INTERVAL (GAP4). Study personnel at each site will enter data from source documents corresponding to a patient's visit into the protocol-specific electronic case report forms (CRFs) in Research Electronic Data Capture (REDCap), a secure web application for building and managing online surveys and databases. Patients will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by site and patient ID numbers. If a correction is required for a CRF, the time and date stamps track the person entering or updating CRF data and creates an electronic audit trail. The Site Principal Investigator is responsible for reviewing all information collected on patients enrolled in this study for completeness and accuracy.

15.2 Study Coordination Centre (SCC)

The designated SCC will be responsible for data processing and maintenance, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH

GCP guidelines for the handling and analysis of data for clinical trials.

15.3 Patient Confidentiality

In order to maintain patient confidentiality, only a patient ID number (and site number where applicable) will identify study patients on study documents.

15.4 Data Quality Control and Reporting

Data validation checks will be implemented and applied to the database by the SCC on a regular basis. All changes to the study database will be documented.

15.5 Archival of Data

The database is safeguarded against unauthorised access by established security procedures; nightly backup of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At pre-specified junctures of the protocol (e.g., production of interim and final reports), data for analysis is locked and cleaned per established procedures.

15.6 Availability and Retention of Investigational Records

To enable evaluations and/or audits from regulatory authorities, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to the International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Trial Agreement, whichever is longer, but at a minimum, all study documentation must be retained for 5 years after the study ends.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Movember should be prospectively notified. The study records must be transferred to a designee acceptable to Movember, such as another investigator, another institution, or to the Movember itself. The Investigator must obtain the Movember's written permission before disposing of any records, even if retention requirements have been met.

15.7 Data Safety Monitoring Committee

A Data Safety and Monitoring Committee will be established to monitor data on an ongoing basis to ensure the safety of the subjects enrolled in this study. The committee will meet yearly until n=50 patients enrolled and then quarterly afterwards to review interim safety and accrual data. In addition, the committee may also meet at the discretion of the Steering Committee. After each review, the committee will make recommendations regarding the conduct of the study. The committee will consist of at least 2 medical experts in the relevant therapeutic area treating MCRPC patients and at least 1 biostatistician.

15.8 Exercise Training Data Collection and Management

Sets, Repetitions and Weight Lifted (Resistance Exercise), as well as Duration, Recovery, Repetitions and RPE (Aerobic Exercise) data will be collected for each exercise performed. Pre-session Bone Pain, Pre-session Fatigue Levels, Post-Aerobic HR, and Post-Session RPE data will be collected for the session overall. All data entries will be monitored by the ECC to ensure high quality data. Exercise data will be recorded and reported via PhysiTrack (an online form). Sessional data will be recorded and reported via REDCap (an online form). This will ensure all data is logged and maintained for each participant accordingly. Please pay careful attention to the data you and your patients enter.

15.9 Self-Management of Exercise Data Collection and Management

Participants will be provided with heart rate monitors to wear at home to monitor adherence to aerobic exercise prescription (heart rate average and maximum) and record session RPE, exercise duration, exercise intensity,

number of repetitions and recovery periods used. Participants will also record the volume of resistance training completed through reporting number of sets, repetitions, and weight lifted. These data will be reported through PhysiTrack (preferred) or on a written form (SOM: Appendix 16a) to be provided to the exercise professional at the on-site visits. **The exercise professional is responsible for entering written forms into PhysiTrack** on behalf of the participant, should this option be used. Select sessional variables will be entered into the online database (REDCap) and will also be monitored by the ECC to ensure high quality data and used for reporting purposes.

15.10 ECC Monitoring of Exercise Testing/Training Data

ECC data monitoring will be conducted by the central Exercise Coordination Centre (ECC) according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP. By signing this protocol, the Investigator grants permission to the ECC to conduct on-site or remote monitoring and/or auditing of all appropriate study documentation. The ECC will review online data at periodic intervals to ensure that exercise assessment visit data are entered regularly and appropriately into the online data system. The ECC will also monitor quantity of missed sessions. The ECC will adhere to a specified policy for alerting sites to exercise data inaccuracies and incompleteness and other problems that may result in protocol violations if not addressed in a reasonable timeframe described in the policy.

15.11 Specimen Collections

Collect, process, store and transport specimens as outlined in the SOM: Appendices 17-19.

16.0 PROTECTION OF HUMAN SUBJECTS

16.1 Informed Consent

Prior to the enrolment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. Patients will be informed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring. Specific guidelines for symptom management are in place to protect the study participant.

All patients will be required to sign a statement of informed consent and research authorisation that meets statutory/CHR guidelines. All patients who meet the eligibility criteria will be considered eligible.

16.2 Potential Risks

Our eligibility criteria and screening procedures are established to exclude individuals for whom blood collection and exercise testing and training are not appropriate. Our screening procedures begin with medical chart review to identify any individuals with any condition or reasons that may prohibit study entry. In-person assessments will also be performed to screen/identify patients for contraindications to exercise. This multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated.

Blood Collection – There are some minor risks associated with a blood draw, i.e., bruising, discomfort, however this procedure is considered to be of minimal risk.

Exercise Training – Exercise training carries a finite risk of an adverse cardiovascular event, muscle strain, ligament sprain or minor skeletal event. All sessions will be supervised by a certified exercise professional.

Risks of research participation – Participation in research involves some loss of privacy. We will do our best to make sure that all personal information gathered for this study is kept private. However, we cannot guarantee total privacy. There is also some risk due to randomisation. The intervention may be more burdensome and may not have a beneficial effect on their prostate cancer prognosis or quality-of-life compared to usual care.

16.3 Potential Benefits

A behavioural treatment strategy such as exercise training among men with prostate cancer may lower the risk of progressive disease as well as confer significant improvements in global cardiovascular function.

Research using blood in this study could lead to medical and scientific products that could improve prevention, diagnosis and treatment of disease.

16.4 Voluntariness of Research

It is stated that taking part in this study is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

16.5 Patient Privacy

Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. Blood and urine samples will be stored with a code linked to the patient's medical record. Every effort will be made to de-identify samples, reports, surveys whenever possible; and items will be physically labelled by an anonymous study-specific ID that is only linked to personal identifiers via a coded-document kept on secure computers, accessible only to study personnel. The results of any research using blood will not be placed in the medical record. The consent indicates that samples and genetic information collected may be shared with other qualified researchers. Such information will not include identifying information such as name.

17.0 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

17.1 Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Good clinical practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of the study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by coded site and patient ID numbers. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient ID number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the patient. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.2 Institutional Review Boards (IRB) and Independent Ethics Committees (IEC)

The protocol, consent forms, any information to be given to the patient (including patient recruitment materials) and relevant supporting information must be submitted to each site's IRB/IEC by the Investigator for review and approval before the study is initiated. Any member of the IRB/IEC who is directly affiliated with this study as an Investigator or as site personnel must abstain from the IRB/IEC vote on the approval of the protocol. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

Investigators are required to promptly report to their respective IRB/IEC all unanticipated problems involving risk to human patients. Some IRBs/IECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study intervention, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with

regulatory requirements and with the policies and procedures established by their IRB/IEC and archived in the site's study file.

Finally, the Investigator will keep the IRB/IEC informed as to the progress of the study, revisions to documents originally submitted for review, annual updates and/or request for re- approvals, and when the study has been completed.

17.3 Protocol Amendments

Any amendments to the protocol must be approved by the Protocol Review Board. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC are notified within five working days (this may vary by country) and within 24 hours to the SCC.

17.4 Informed Consent Form

Informed consent will be obtained in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy. The master ICF will be provided to each site. The Sponsor or its designee must review and approve any proposed deviations from the master ICF proposed by a site before IRB/IEC submission. The final IRB/IEC-approved consent forms and any revisions to the consent form during the study must be provided to Sponsor for regulatory purposes. The ICFs must be signed by the patient or the patient's legal representative before his participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legal representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated consent forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. Patients must be re-consented to the most current version of the consent forms during their participation in the study. For any updated or revised consent forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised consent form for continued participation in the study.

17.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the World, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational intervention, the SCC and ECC should be informed immediately, who will inform Movember. The local IRB should also be informed. The Investigator will inform the SCC and ECC of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

17.6 End of Trial in All Participating Countries

Patients will remain in the study until development of unacceptable toxicity, withdrawal of consent, death, or end of study. Patients discontinuing the on-treatment phase will enter the survival follow-up period and remain on study until death, loss of follow-up, or withdrawal of consent, whichever comes first.

With an estimated accrual duration of 5 years, it is assumed that patients are expected to be followed for a minimum of approximately 41 months beyond Last Patient In (LPI) for the key primary endpoint of OS and approximately 9 months beyond LPI for the secondary endpoint of PFS. This corresponds to total projected study duration of approximately 77 months.

If the study is not terminated beforehand per the recommendation of the IDMC, the end of trial in all participating

countries will be defined as the time at which the primary endpoint of OS has been met.

17.7 Movember Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, intervention safety problems, or at the discretion of Movember. If study is prematurely terminated or discontinued, Movember will promptly notify the Investigator. After notification, the Investigator must notify the respective IRB/IEC, and contact all participating subjects within a 4-week time period. As directed by Movember, all study materials must be collected and all CRFs completed to the greatest extent possible.

17.8 Publications

Publication of study results is discussed in the Clinical Trial Agreement. Details regarding production of manuscripts and conference presentations will adhere to the International Committee of Medical Journal Editors (ICMJE) requirements for authorship and contributorship. http://www.icmje.org/ethical_1author.html

18.0 REFERENCES

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