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

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

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:

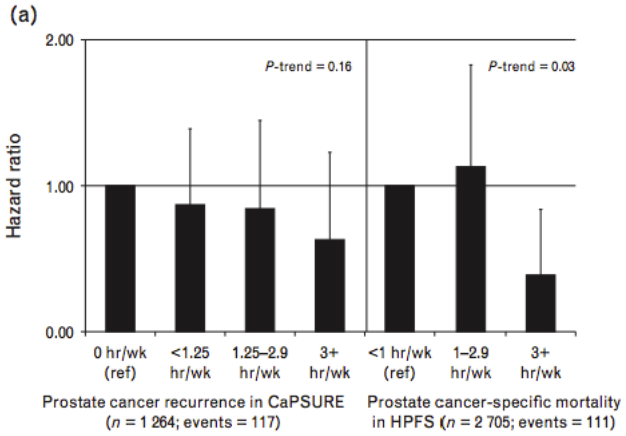

Figure 1. Duration of vigorous physical activity after diagnosis of non-metastatic prostate cancer and risk of prostate cancer recurrence and mortality in two distinct cohorts. Error bars represent the upper bound of the 95% confidence interval (Kenfield SA et al, *J Clin Oncol*, 2011; Richman EL et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

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

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.

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

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:

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

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

	≥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

TABLE OF CONTENTS

SECTION

APPENDICES

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.**

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).

- **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,

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

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

- 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

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,