Exercise during Active Surveillance for Prostate Cancer: The ERASE Trial

Version: 2.0
Creation/Revision Date: December 18, 2017
Clinical Trial Registration: NCT03203460

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1 Study Summary/ Synopsis

Title	Exercise during Active Surveillance for Prostate Cancer
Short Title	The ERASE Trial
Protocol Number	-
Phase	Phase 2
Methodology	Randomized, usual care control, two-armed, parallel design
Study Duration	18 months (January 2018 – June 2019)
Study Center(s)	Single-center
Objectives	To examine the effects of exercise in prostate patients undergoing active surveillance
Number of Subjects	66
Accrual rate and Justification	Considering >1,500 potentially eligible patients in the registry and approximately 10 new patients placed on active surveillance per month, this project will require only a 4% response rate to achieve our targeted sample size.
Diagnosis and Main Inclusion Criteria	Prostate cancer patients initiating or continuing active surveillance with no plans for treatment for prostate cancer in the next 6 months
Investigational product, treatment or intervention	A structured exercise program – Supervised high-intensity interval aerobic exercise, 3 sessions/week, 30 minutes per session
Duration of administration	12 weeks
Reference therapy	Usual care group – Standard active surveillance protocol (no structured exercise program)
Statistical Methodology	ANCOVA – To detect differences between-group changes before and after the exercise intervention

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3 Introduction

3.1 Background and Rationale

Prostate cancer (PCa) is the most common cancer in Canadian men with over 21,000 new cases diagnosed each year[1]. Conventionally, a PCa diagnosis is treated immediately by radical prostatectomy, radiation therapy, and/or hormonal therapy[2]. These treatments improve overall survival; however, they also are expensive and often cause serious side effects such as sexual and urinary dysfunction, fatigue, loss of lean body mass, muscle weakness, and poor quality of life[3,4]. Consequently, there is a desire to only offer these radical treatments to men who will obtain a clear clinical benefit. In recent years, a subset of men with PCa have been identified who have a very low risk of disease progression and death from PCa. These men are unlikely to obtain a clear clinical benefit from immediate radical treatments. To address this issue, a clinical practice called "active surveillance (AS)" has emerged and is being offered to men with low-to-moderate grade PCa. In AS, men with low risk PCa do not receive any immediate treatments but are monitored closely for any signs of tumour growth. Curative medical treatments are offered only if the disease progresses[5]. The obvious advantage of AS is that it allows early-stage PCa patients to avoid treatment-related side effects without compromising their survival[6]. Moreover, AS represents a considerable cost savings over radical treatment[7-9], estimated at $96.1 million per year in Canada[10]. Due to these advantages, the number of PCa patients being offered AS in Canada has increased substantially[11].

Unfortunately, many men with PCa on AS will eventually experience disease progression and require radical treatments. Approximately 30% of men on AS will have radical treatments within three years and about 55% will have treatment within 10 years. Moreover, even if these men do not experience an objective progression of their disease, they may experience a fear of cancer progression based on the fact they have an untreated tumor with a high chance of progressing[12]. Fear of cancer progression and uncertainty of illness are associated with anxiety and poor quality of life in AS patients[13] and may even prompt these men and their doctors to opt for radical treatments as a way of managing the fear and anxiety[14]. **Cost-effective interventions that can slow tumor progression, manage fear of cancer progression, and prepare PCa patients on AS for impending radical treatments would be highly beneficial**. To date, however, no such interventions are offered as standard of care in this clinical setting.

Lifestyle Interventions in Prostate Cancer Patients on Active Surveillance

One promising line of inquiry is examining the potential role of lifestyle interventions in men with PCa on AS. For example, one study investigated the effects of a year-long intensive lifestyle program on PCa progression and health-related quality of life in 92 PCa patients on AS (Prostate Cancer Lifestyle Trial, PCLT)[15,16]. The intervention was comprised of a vegan diet, moderate-intensity aerobic exercise (walking 30 minutes per day for 6 days per week), stress management, and a weekly 1-hour support group session[17]. At 3 months, an interim analysis only for the intervention group showed significant improvements in cardiovascular risk factors

such as body mass index, abdominal obesity, blood pressure, and lipid profile as well as several indicators of psychological functioning including mental component summary, intrusive thoughts, and avoidance[18]. Total and free prostate-specific antigen (PSA) levels were not significantly improved although the percentage of free PSA showed a non-significant but clinically meaningful change[18]. After one year of intervention, in addition to similar improvements in cardiovascular risk factors, total PSA was significantly reduced by 4% in the intervention group while it increased by 6% in the control group[15]. Also, the growth of LNCaP PCa cells, androgen-sensitive human prostate adenocarcinoma cells, was inhibited 8-times more in the intervention group compared to the control group[15]. Moreover, overall health-related quality of life increased in the intervention group compared to the control group although no significant differences were found in other subscales such as physical- and mental-health, perceived stress, and sexual function[16]. After 2 years of follow-up for clinical events, they reported that 2 of 43 (5%) patients in the intervention group and 13 of 49 (27%) patients in the control group had proceeded to radical PCa treatments (prostatectomy, radiotherapy, or hormone therapy), while no significant differences in PSA levels and the number of other clinical events were found[19]. After 5 years of follow-up, telomere length increased in the intervention group and decreased in the control group while PSA and telomerase activity were not significantly different between groups[20]. Overall, this study provided promising evidence that an intensive lifestyle intervention in PCa patients on AS may slow the progression of the disease, improve some aspects of quality of life, and decrease the rate of radical treatments.

Another randomized controlled trial in 26 men with PCa undergoing AS tested the effects of a six-month combined whole-grain diet and vigorous exercise program[21]. The exercise program included non-supervised aerobic exercise three times/week for 45 minutes/session targeting 70% of maximal heart rate (HR) in addition to at least 10,000 steps daily. The combined intervention resulted in an improvement in peak oxygen consumption (VO_{2peak}) in the intervention group compared to the control group, however, no other significant differences were found for body composition, cardiometabolic outcomes, or PSA after six months of intervention.

Another intervention study with 40 overweight or obese men with PCa provided a presurgical weight loss intervention consisting of diet and physical activity[22]; however, only feasibility outcomes have been reported and the focus of the study is on men electing radical prostatectomy. Several other cohort, cross-sectional, and systematic review studies have also concluded that lifestyle interventions are a promising avenue of research for improving tumor outcomes in PCa patients on AS[23-25]. As might be expected, however, these early preliminary studies have limitations including few randomized controlled trials, small sample sizes, unsupervised exercise interventions, and the testing of packaged lifestyle interventions that do not allow the disentangling of the key active components of the intervention.

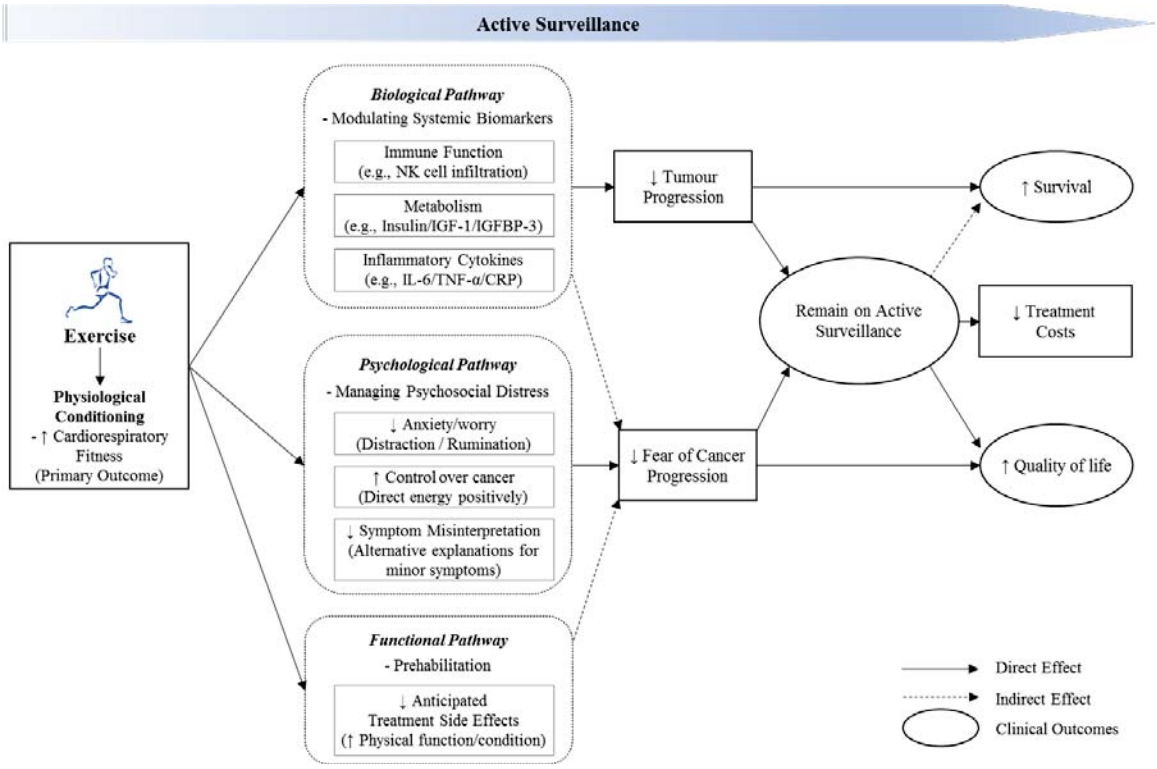
Exercise is one of the key components of a lifestyle intervention that may have independent effects on clinical outcomes in PCa patients on AS; however, no study to date has tested the effects of an isolated exercise intervention. Exercise has been shown to delay the progression of prostate tumors in animal models[26-28], which is

mainly attributed to alterations in immune function[29]; however, these findings have not been confirmed in men with PCa. Moreover, exercise has been shown to improve health-related fitness[30-33], physical functioning[31-37], body composition[31-34,37], fatigue[32-34,36], and quality of life[32-34,36,38] during and after radical PCa treatments, but no study to date has focused on the AS setting or examined fear of cancer progression – the psychological construct most likely to result in unnecessary medical intervention. Furthermore, exercise may help prepare PCa patients for radical treatments (i.e., prehabilitation)[39-41] but current studies are only preliminary and none have focused on PCa patients on AS. **Our novel idea is that exercise may be a cost-effective intervention that slows the growth of PCa tumors and manages fear of cancer progression, thereby allowing these men to remain on AS longer or even indefinitely**. **Moreover, exercise may help buffer the negative effects of radical treatments in the >50% of men who will ultimately require medical treatments**.

Theoretical Model (**Figure 1**)

We propose that exercise—sufficient to improve cardiorespiratory fitness may benefit men with PCa on AS through three distinct pathways: (1) In the "biological pathway", exercise may have a direct effect on suppressing tumour growth thereby delaying or preventing the need for radical treatments in AS patients. Scientific evidence shows that exercise can modulate cancer-related circulating markers in various mechanisms[42-44] such as immune function[45-48] (e.g., natural killer (NK) cell mobilization and infiltration into cancer cells), metabolism[49,50] (e.g., insulin and insulin-like growth factor(IGF)-axis), and inflammation[51] (e.g., interleukin-6(IL-6) from myokines, tumour necrosis factor (TNF)-α, high-sensitive c-reactive protein(hs-CRP)), which creates an anti-tumour microenvironment, resulting in a delay or even reversing of tumour progression[29]. (2) In the "psychological pathway", exercise may reduce the fear of cancer progression through several psychological mechanisms such as providing a distraction and a sense of control, reducing anxiety/cancer worry and intrusive thoughts, and providing an alternative explanation for everyday symptoms such as mild pain, fatigue, and soreness that may be misinterpreted as signs of cancer progression[12,13]. These psychological benefits may also improve quality of life and prevent these men from requesting radical treatments as a way of managing their anxiety and fear of cancer progression. (3) In the "functional pathway", exercise can improve patients overall physical function and condition such as aerobic fitness, muscular strength, body composition, and activities of daily living. Improvements in these factors may help reduce the impact and complications of radical treatments. If PCa patients on AS feel they are better prepared physically for radical treatments and will experience fewer side effects and complications, they may also reduce their fear of cancer progression. **In summary, we propose that exercise in PCa patients on AS may suppress tumour progression and reduce fear of cancer progression which may help these men remain on AS longer. A longer time on AS would mean improved survival and quality of life for these men and lower financial costs for society.**

Figure 1. Proposed Effects of Exercise during Active Surveillance in Prostate Cancer Patients



Principles Guiding the Selection of the Exercise Training Intervention

In terms of maximizing the potential benefits of exercise in AS patients, a body of evidence supports that higher-intensity exercise programs often produce greater health benefits compared to moderate-intensity continuous training[52,53]. High-intensity interval training (HIIT) aerobic exercise is a type of high-intensity exercise, alternating short periods of intense exercise and active recovery. HIIT has been shown to induce better outcomes such as cardiopulmonary fitness and cardiovascular disease (CVD) risk factors in patients with heart disease, compared to traditional moderate-intensity exercise[53-56]. Moreover, HIIT is not only feasible and safe in several types of cancer patients but also beneficial in improving physical fitness and mental health[57-60]. Finally, given that higher-intensity exercise may be required to induce a sufficient increase in NK cell infiltration to kill tumour cells (up to 60% in animal models), it is plausible that HIIT may be the optimal intervention for boosting cancer surveillance and tumor suppression in AS patients[29,61].

3.2 Compliance Statement

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

3.3 Description of the population to be studied

The population to be studied in the ERASE Trial will be men with PCa initiating or continuing AS. These patients are men diagnosed with low- or favorable intermediate grade localized PCa. These patients do not receive immediate PCa treatment, but visit the clinic for regular check-ups, typically every three months for PSA and DRE and every 18 months for prostate biopsy, until the PCa becomes significant where treatment is necessary.

3.4 Trial Objectives and Purpose

The overall goal of the Exercise during Active Surveillance for Prostate Cancer (ERASE) Trial is to examine the effects of exercise in PCa patients undergoing AS. The primary objective is to examine the effects of HIIT on VO_{2peak} in PCa patients undergoing AS. The secondary objectives are to examine the effects of HIIT on: (1) other health-related fitness outcomes including physical function and body composition, (2) tumor-related serum biomarkers including immune, metabolic, and inflammatory markers, and (3) patient-reported outcomes including fear of cancer progression, quality of life, and symptoms. The exploratory objectives are to examine the effects of HIIT on indicators of cancer progression including tumour volume and PSA levels.

3.5 Trial Design

The ERASE Trial will be a prospective, single center, two-armed, phase II randomized controlled trial at the University of Alberta, Cross Cancer Institute (CCI), and Northern Alberta Urology Centre (NAUC) in Edmonton, Alberta. Ethics approval will be obtained from the Health Research Ethics Board of Alberta-Cancer Committee (HREBA-CC) prior to commencing the trial.

3.6 Trial Endpoints

3.6.1 Primary Endpoints

The primary endpoint of the ERASE trial is VO_{2peak}.

3.6.2 Secondary Endpoints

The secondary endpoints are (1) tumour-related immune, metabolic, and inflammatory biomarkers, (2) patient-reported fear of cancer progression, quality of life, anxiety, depression, fatigue, perceived stress, self-esteem, and PCa-specific symptoms, (3) physical function, and (4) body composition.

3.6.3 Exploratory Endpoints

The exploratory endpoints are tumour progression outcomes using PSA, DRE, and endo-rectal multiparametric magnetic resonance imaging (MP-MRI).

3.7 Steps to Minimize Bias

Participants will be randomly assigned to either the exercise group or the usual care group in a 1:1 ratio after baseline assessment. The randomization scheme will include stratification for the length of time on AS (<6 months versus ≥6 months) and variable block sizes of 4 to 8. The allocation sequence will be produced by computer-generated random numbers and concealed from staff involved in recruitment and baseline testing. Given the nature of the exercise intervention, it is not possible to blind participants and interventionists to group allocation. Outcome assessors, however, will be blinded to group allocation for the primary outcome of VO_{2peak} and the secondary/exploratory outcomes of physical function, body composition, biomarker assays, and tumour progression. The assessors will also follow the detailed protocol to minimize any potential bias in measurements.

3.8 Trial Treatment

The treatment group will be provided a 12-week, supervised, HIIT aerobic exercise program. The type of exercise will consist of alternating vigorous and low intensity interval running or walking performed on a treadmill. Exercise sessions will be provided three times per week and each session will last approximately 30 minutes. The intensity of exercise will be determined by treadmill speed and/or incline and will be prescribed and gradually increased at specific workloads corresponding to percentage of VO_{2peak} measured at baseline. An exercise session of 1) warm-up (5 min at a workload corresponding to 65% of VO_{2peak}), 2) high-intensity exercise phase (2 min at an increasing workload corresponding to VO_{2peak} at 85% in the 1st -4th week, 90% in the 5th -8th week, and 95% in the 9th-12th week) followed by recovery phase (2 min at a workload corresponding to 35-45% of VO_{2peak}), 3) four more sets of high-intensity exercise and recovery phases adding 1 additional interval every 4 weeks, and 4) cool-down (5 min at a workload corresponding to 40% of VO_{2peak}). For the purpose of quantifying exercise intensity, patient-reported exertion levels will be recorded using the Borg's Rating of Perceived Exertion Scale and HR will continuously be monitored using a HR monitor at the end of each interval.

3.9 Trial Duration

The expected participant flow in the ERASE Trial is illustrated in the **Appendix – Figure 2**. In brief, after randomization, participants will be provided with an exercise intervention for 12 weeks and then receive postintervention assessment and long-term follow-ups for exercise behaviour at 6 and 12 months.

3.10 Discontinuation Criteria

Discontinuation criteria include (1) receiving any invasive PCa treatment during the 12-week intervention period due to tumour progression, patients' preference, and/or any reasons determined by referred oncologists, and (2) any intolerable adverse event or intercurrent illness associated or not associated with the study intervention and/or assessment, where patients are considered to be unable to continue participating in the intervention.

3.11 Source Data

Patients' medical information will be abstracted from the NAUC patient registry, including tumor-related information, complications or comorbidities. Ethics approval from the HREBA-CC will be obtained for the acquisition of the patient data from the registry. Demographic and behavioral information will be obtained using a self-report questionnaire at baseline. The questionnaire will ask age, ethnicity, education, marital status, income, employment status, smoking, and alcohol consumption.

4 Methodology: Participants, Interventions and Outcomes

4.1 Consent

All patients will be informed about

- The aims of the study
- The possible adverse events
- The procedures and possible hazards to which the patient will be exposed
- The mechanism of treatment allocation
- Strict confidentiality of any patient data
- Medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The consent is given as a separate document dated and version controlled to this protocol. The informed consent documents are to be completed based on the template provided from the HREBA-CC and submitted to the ethics committee for approval. It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he wants to and this will not have any impact on the patient's subsequent care. Documented informed consent will be obtained for all patients included in the study. The written informed consent form will be signed and personally dated by the patient or by the patient's legally acceptable representative.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Men will be eligible for the trial if they (1) are ≥ 18 years old, (2) diagnosed with low or favorable intermediate grade localized PCa defined as PSA less than 10, Gleason Score 3+3 or 3+4 with low volume, and digital rectal examination (DRE) of T1C or T2A, (3) initiating or continuing AS with no plans for treatment in the next 6 months, (4) receive medical clearance to perform maximal aerobic exercise testing and HIIT as determined by their treating urologist, the Physical Activity Readiness Questionnaire, and a Certified Exercise Physiologist, and (5) willingness to attend a

12-week supervised exercise training program at the University of Alberta or continue with their usual activity.

4.2.2 Exclusion Criteria

Patients will be excluded if they (1) have any plans for treatment in the next 6 months, (2) have any uncontrolled medical conditions that could be exacerbated with HIIT, (3) have contraindications for cardiopulmonary stress and/or physical fitness, and/or (4) are currently exercising defined as >0 minutes of vigorous intensity exercise and >150 minutes of moderate intensity exercise in a typical week over the past month.

4.2.3 Withdrawal Criteria

Withdrawal criteria include: (1) patient's self-withdrawal to permanently discontinue study treatment and withdraw from the study anytime for any reason, and following study intervention discontinuation, patients will have protocol-required safety and long-term follow-up assessments unless the patient specifically declines further follow-up), 2) having any invasive PCa treatment and/or any intolerable adverse event associated or not associated with the study intervention and/or assessment, and 3) gross noncompliance with protocol where the investigator requests permanent discontinuation of the study intervention in the event of a major protocol deviation, lack of cooperation, or complete noncompliance).

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 consent document. 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. Reasons for stopping the intervention will be recorded and reported.

4.3 Sample Size

4.3.1 Sample Size Calculation

A sample size of 60 participants (30 per group) provides 80% power using a two-tailed alpha <0.05 to detect a clinically meaningful increase of a 1 metabolic equivalent task (MET = 3.5 ml/kg/min) on our primary outcome of VO_{2peak} assuming a standard deviation of 5.6 ml/kg/min and adjustment for baseline value and other prognostic covariates[62]. An increment of a 1 MET in cardiopulmonary fitness, equivalent to approximately 1km/h higher running/jogging speed, is shown to correspond to an improvement of 13% and 15% in overall and CVD-related survival, respectively[63]. Considering a potential drop-out rate of <10% based on our previous exercise oncology trials[64-67], a total of 66 participants (33 per group) will be randomized. This power will also be sufficient for detecting differences in our

secondary biomarkers and patient-reported outcomes if the effects are moderate (i.e., a standardized effect size of approximately ≥ d=0.60). This power is not sufficient for detecting potentially meaningful differences in any of the exploratory clinical outcomes. Given that the purpose of this phase II trial is to inform phase III trials, the patient-reported and clinical outcomes will also be interpreted for potential clinical significance based on the direction and magnitude of numerical differences. For our main patient-reported outcome of interest—QoL assessed by the QLQ-C30—we will judge a clinically meaningful effect to be a between-group difference of 10 points[68]. For our primary clinical outcome of interest—progression to radical treatment—we will judge a clinically meaningful effect to be a between group absolute difference of 10%.

4.3.2 Accrual Period

The target accrual number is 66 and we expect to recruit this targeted number of patients over 8 months (March – August 2018). Recruitment will be through the NAUC at the Kaye Edmonton Clinic. Currently, the NAUC has more than 1,500 PCa patients on AS in the registry and typically puts approximately 10 new patients on AS per month. We will mail out an invitation to the study and interested patients will contact our research team.

We have used this mailed invitation approach to recruit to previous randomized supervised exercise trials and were able to recruit 53 of 370 (14%) breast cancer survivors[65], 22 of 324 (7%) lymphoma survivors[66], 30 of 502 (6%) PCa survivors[64], and 63 of 948 (7%) testicular cancer survivors[69]. To achieve our targeted sample size of 66 in the ERASE trial will require only a 4% response rate from the 1,500 PCa patients on AS currently in the registry.

4.4 Recruitment

Patients will be screened for eligibility through the patient registry and mailed a recruitment package consisting of a cover letter explaining the details of the study and a consent form. All interested participants will then be asked to phone or email the research coordinator to express their interest and arrange a phone-based screening appointment. Those patients who are eligible and agree to participate will be asked to provide informed consent and complete a questionnaire, blood draw, and physical fitness and functioning tests.

4.5 Interventions

4.5.1 Treatment

<u>Exercise Group</u>

Patients randomized to the exercise group will be provided with standard AS care and asked to complete a 12-week, supervised HIIT program in addition to any moderate intensity exercise they were previously doing (**Appendix - Figure 3; HIIT Protocol**). The type of exercise will consist of alternating vigorous- and low-intensity intervals performed on a treadmill. The intensity of exercise will be modified by changing treadmill speed and/or grade prescribed at specific workloads

corresponding to percentage of VO_{2peak} measured at baseline. Exercise frequency will be three times per week and each session will last approximately 30 minutes. The detailed exercise program consists of 1) warm-up (5 min at a workload corresponding to 65% of VO_{2peak}), 2) high-intensity exercise phase (2 min at an increasing workload corresponding to VO_{2peak} at 85% in the 1st -4th week, 90% in the 5th -8th week, and 95% in the 9th-12th week) followed by recovery phase (2 min at a workload corresponding to 35-45% of VO_{2peak}), 3) four more sets of high-intensity exercise and recovery phases adding 1 additional interval every 4 weeks, and 4) cool-down (5 min at a workload corresponding to 40% of VO_{2peak})[54,55]. For the purpose of quantifying exercise intensity, patient-reported exertion levels will be recorded using the Borg's Rating of Perceived Exertion Scale[70] and HR will continuously be monitored using a HR monitor (Polar U.S., Woodbudy, NY) at the end of each interval. We have recently tested this HIIT protocol in testicular cancer survivors and found large improvements in VO_{2peak} and cardiovascular risk factors[69].

Usual Care Group

Patients randomized to the usual care group will be provided with standard AS care. Currently, the standard AS care at our site does not include any formal exercise program or recommendation. Consequently, participants in the usual care group will be asked not to initiate any vigorous intensity exercise program or to increase their moderate intensity exercise from baseline during the 12 week study. After the post-intervention assessments, patients in the usual care group will be offered a 4 week supervised exercise program at our facility or referred to a 12 week community-based program called the Alberta Cancer Exercise (ACE) program.

After the 12-week study period, participants in both exercise and usual care groups will be followed up at 6 and 12 months for their exercise behaviour assessed using a modified version of the Godin Leisure-Time Exercise Questionnaire[71].

4.5.2 Study Calendar

	Before Treatment (Baseline)	Post-Treatment (At 12-week)	Follow-up 1 (At 6-month)	Follow-up 2 (At 1-year)
Consent	X			
Medical History & Information	X			
Demographics	X			
Treatment (HIIT)	X			
Cardiorespiratory Fitness Test	X	X		
Tumour-related Biomarkers Test	X	X		
Physical Function Test	X	X		
Body Composition Test	X	X		
QOL and Psychosocial Questionnaires	X	X	X	X
Tumour Progression	X	X	X	X
Exercise Behaviour	X	X	X	X

4.5.3 Medications/Treatments Permitted

Patients will not have any medication-, diet-, and/or supplement-related restriction before and/or during the trial.

4.5.4 Monitoring Compliance

During the 12-week intervention period, exercise adherence to the prescribed exercise program will be monitored and recorded based on attendance at the scheduled exercise sessions and completion of the intensity, duration, and number of intervals during each exercise session. Strategies to maximize adherence will include appointment-based sessions, flexible scheduling, individualized exercise program, supervision by certified clinical exercise physiologists, free parking, and use of the Behavioural Medicine Fitness Centre (BMFC) which is available only to cancer patients participating in clinical exercise trials. Any missed sessions will trigger a telephone call with a rescheduling of the exercise session as soon as possible. Using these strategies, we have achieved high exercise adherence rates in previous supervised exercise trials including 98% in breast cancer survivors[65], 79% in PCa patients on androgen deprivation therapy[36], 92% in lymphoma survivors[66], 88% in PCa patients receiving radiation therapy[33], 98% in PCa survivors[64], and 99% in testicular cancer survivors[69].

4.6 Outcomes

4.6.1 Primary Outcomes

The primary outcome of this phase II trial is cardiorespiratory fitness, which is a powerful surrogate for cancer-specific and overall survival. Cardiorespiratory fitness will be assessed as VO_{2peak} by a maximal exercise stress test using the Modified Balke Exercise Test protocol[72]. Participants will be provided with detailed and verbal instruction about the procedure of the test and asked for abstaining from alcohol, caffeine, and exercise within 24 hours prior to the test. Participants will be familiarized with the mouthpiece and testing equipment by walking on the treadmill for approximately 5 minutes, followed by 5minute of rest, and resting HR, blood pressure (BP), and health conditions will be measured before the test to stabilize resting metabolic values. After the warm-up (2.5 – 4.0 mph; 0% grade; 2 minutes), participants will walk at a constant speed (3.5 mph) from 6% to 22% grade in 2% increment each minute. During the test, oxygen uptake and HR will be measured continuously. VO_{2peak} is defined as the highest oxygen-uptake value recorded during the test and will be quantified where participants reach a plateau in oxygen consumption, respiratory exchange ratio of 1.1 or above, or 19 to 20 on the Borg rated perceived exertion[70]. After the test, HR will be measured for an additional 6 minutes of recovery (1st minute standing plus 5 minutes of active recovery). One-minute HR recovery will be calculated as the HR-difference between peak exercise and following one minute of treadmill-standing immediately post-test. VO_{2peak} will be expressed relative to body mass (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$; primary) and absolute terms (litres/min).

4.6.2 Secondary Outcomes

Circulating biomarker outcomes

Fasting blood will be taken in the morning following an overnight fast where there was no food intake after 8pm and a minimum of 48 hours since the last vigorous exercise session. Blood draws can occur on the same day as the exercise assessment, prior to the commencement of the assessments. Serum blood will be drawn in the 6.0mL red top tube, clotted for 30-60minutes, and spun for 20 minutes at 2860 rpm. Then, 0.75mL of serum will be transferred to each of the four cryovials provided. Two 10.0 mL EDTA tubes will be collected and one spun for 10 minutes at 2860 rpm within one hour of collection and 1.0mL of plasma will be transferred to a secondary tube to cryovials. The remaining blood from the second tube will be centrifuged and on Ficoll gradients and the peripheral blood mononuclear cells (PBMC) Ficoll isolated[73] and frozen in RPMI 1640 media containing 20% FCS and 10% DSMO and stored in liquid nitrogen. Samples will be stored or shipped frozen at -70°C and the Biological Sample Log will be completed. Frozen PBMC will be warmed in a 37 ^{o}C water bath for 3 minutes, in media and incubated overnight at 37 ^{o}C in the presence of 5% CO[73] and then used to identify NK cells (CD3-CD16+CD56+) using flowcytometry and to measure NK activity using a flow cytometry method[74] that has been validated for previously frozen PBMC. This assay incubates K562 cells with 2×10^5 effector cells (NK cells) and measures CD107a expression which correlates with the release of perforin and other cytolytic granules that induce death of tumour cells. Metabolic biomarkers, including serum insulin, glucose, IGF-1, IGFBP-3, and adiponectin, will be assessed using the ELISA kits on frozen samples. Inflammatory markers will include proinflammatory cytokines such as IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, and hs-CRP, assessed using a multi-ligand analysis system according to commercial kit instructions on frozen plasma or serum.

Patient-reported outcomes

1) Fear of cancer progression will be assessed using the 8-item Cancer Worry Scale[75] and the 9-item Fear of Cancer Recurrence Inventory[76]. 2) Quality of life will be assessed using the 30-item European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire-C30[77]. 3) PCa-specific health-related quality of life and symptoms including urinary incontinence, sexual dysfunction, and bowel dysfunction will be assessed using the 26-item Expanded Prostate Cancer Index Composite-26[78]. 4) General anxiety and prostate-specific anxiety will be assessed using the 10-item Spielberger State-Trait Anxiety Inventory[79] and the 18-item Memorial Anxiety Scale for Prostate Cancer[80], respectively. 5) Depression will be measured using the 10-item Center for Epidemiologic Studies Depression Scale[81]. 6) Fatigue will be assessed using the 13-item Functional Assessment of Cancer Therapy-Fatigue[82]. 7) Perceived stress will be assessed using the 14-item Perceived Stress Scale[83]. 8) Self-esteem will be assessed using the 10-item Rosenberg Self-Esteem Scale[84]. [71]9) Motivation to exercise will be assessed based on the Theory of Planned Behaviour constructs (instrumental and affective attitudes, subjective norms, intention and perceived control)[85].

Physical function

Physical function will be assessed using the Senior's Fitness Test[86] which includes lower body strength (chair stand), upper body strength (arm curl), lower body flexibility (chair sit and reach), back scratch (upper body flexibility), and 8-foot up and go (agility) tests.

Anthropometric measurements

Height, body weight, and waist and hip circumferences will be measured using height and weight scales and a tape measure, respectively.

4.6.3 Exploratory Outcomes

Tumor progression outcomes

Tumour progression will be assessed using PSA and DRE. Total PSA will be measured by two-site automated immunoluminometric assays on Liason (sandwich principle) (Byk-Sangtec Diagnostica, Dietzenbach, Germany). Both assays, calibrated to the Stamey Reference Standard, will employ two different but highly specific monoclonal antibodies for coating of the solid phase (magnetic particles) and for the tracer. The concentration of the antigen in the samples will be measured in relative light units by way of the chemiluminescence reaction induced and the light signal produced, which is directly proportional to the antigen concentration. Mean intra- and inter-assay coefficient of variations of the assays is lower than 8.0 %. DRE will be conducted by the physician inserting a gloved, lubricated finger into the rectum and examining the prostate for any irregularities in size, shape, and texture.

5 Methodology: Data Collection, Management, and Analysis

5.1 Data Collection Methods

5.1.1 Case Report Forms (CRFs)

Patient data related to the study will be recorded on the CRFs. Patients will not be identified by name on the CRFs or any study documents, but will be identified by participant ID numbers. If a correction is required for a CRF, the time and date marks track the person entering or updating CRF data.

5.2 Statistics

5.2.1 Description of Statistics

Analyses of covariance will be performed to compare the between-group differences at post-intervention after adjustment for the baseline value of the outcome and potential covariates. All statistical analyses will include all patients with baseline and follow-up data and will be conducted based on the intention-to-treat principle. If missing data is <10% as expected we will conduct a complete case

analysis. If missing data is >10%, we will employ a multiple imputation missing data strategy[87].

5.2.2 Level of Significance to be used

All analyses will be considered statistically significant with a 2-tailed α=0.05.

5.3 Criteria for the Termination of the Trial

The investigator has the right to close their study at any time. The sponsor (Alberta Health Service-CCI) has the right to close this study (or, if applicable individual segments thereof [e.g. treatment arms, centers]) at any time, which may be due but not limited to the following reasons:

5.3.1 Futility

If the study conduct (e.g. recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame the trial will be terminated.

5.3.2 Safety

If risk-benefit ratio becomes unacceptable owing to, for example,

- Safety findings from this study (e.g. SAEs);
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. HREBA-CC; competent authorities; study centers) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner]

5.4 Deviations

Given that we will strictly follow the statistical plan as described in the protocol, we do not expect that there will be any deviations from the original statistical plan.

5.5 Analysis

All subjects who are randomized will be included in the analyses using the intention-to-treat analysis approach. There will be no interim analyses.

5.6 Data Management

5.6.1 Data Accounting

All missing, unused, or spurious data will be cross checked between researchers who are in charge of data management. If missing data is <10% as expected we will conduct a complete case analysis. If missing data is >10%, we will employ a multiple imputation missing data strategy[87]

5.6.2 Confidentiality of Trial Documents and Patient Records

Data collection forms will contain names, initials, date of birth, and study ID numbers. These are for filing and data entering purposes only and all data entered and analyzed will use study ID numbers. All data will be entered into a database on a password-protected computer. Only the research team members will have access to the password. Interpretation of the results will be in group data format and participants will not be identified.

5.6.3 Retention of Patient Records and Study Files

All data will be securely stored in accordance with Tri-Council and University guidelines. Following data analysis, identity records will be destroyed and identifiers will be removed from the data. At the University of Alberta, researchers are required to keep data for 5-years following the publication of data. The data will be anonymous and stored in a locked office for 1-2 years post completion of study during preparation of manuscripts. After publication, the data will be stored in a locked storage facility managed by the Faculty of Physical Education and Recreation at the University of Alberta. Good Clinical Practice Guidelines and Health Canada and FDA regulations state that clinical trial records must be maintained for 25 years, and thus the data from this trial will be stored in a locked storage facility managed by the Faculty of Physical Education and Recreation at the University of Alberta. Following the 25 year time period, the data will be destroyed by shredding which will be overseen by the Behavioral Medicine Lab. Electronic copies will also be destroyed at this point in time.

6 Quality Control, Quality Assurance and Monitoring

6.1 Direct Access to Source Data/Documents

Clinical trial audits are performed to provide assurance that the rights, safety and wellbeing of patients are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator will permit trial-related monitoring, audits, HREBA-CC, and regulatory inspections, providing direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as

hospital patient charts and investigator study files). All site facilities related to the study conduct could be visited during an audit. The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

6.2 Data Monitoring

6.2.1 Efficacy/Safety

6.2.1.1 Assessment of Efficacy

6.2.1.1.1 Efficacy Parameters

Efficacy of the study will be determined by a 1-MET (3.5 ml/kg/min) difference of between group changes in the primary outcome of VO_{2peak}. The secondary outcomes of psychosocial distress, biological parameters, physical function, body composition, and tumour progression variables will also be considered to determine the efficacy of the study.

6.2.1.1.2 Methods and timing for assessing, recording, and analyzing of efficacy parameters.

The methods for assessing the efficacy parameters are described in detail in the **4.6. Outcomes**. The timing of assessments for efficacy parameters will be conducted at baseline, postintervention (at 12-week), the first follow-up (at 6-month), and the second follow-up (at 1-year) and detailed timing of assessment for each parameter are described in **4.5.2. Study Calendar**.

6.2.1.2 Assessment of Safety

6.2.1.2.1 Safety Parameters

For assessment of safety for the HIIT intervention, symptom-limited cardiopulmonary exercise test during the screening period will be conducted. Vital signs or any physical symptoms and concomitant medications will be continuously obtained during and after every exercise intervention sessions.

Adverse event(AE)s will be assessed at every clinic visit and the following details recorded on the case report form, including type, severity, relationship to exercise intervention, expectedness, timing, action taken (if any) and outcome. In this trial, the study intervention is a supervised high-intensity interval aerobic exercise program. All potential participants will be screened via their medical charts as well as through in-person assessments to assess cardiovascular and functional contraindications to exercise. Our multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated.

Absolute indications for stopping exercise (both testing and training) are: 1) suspicion of a myocardial infarction or acute myocardial infarction (heart attack), 2) onset of moderate-to-severe angina (chest pain), 3) drop in systolic blood pressure

(SBP) below standing resting pressure or drop in SBP with increasing workload accompanied by signs or symptoms or hypotensive response resulting in SBP <60mmHg, 4) signs of poor perfusion (circulation or blood flow) including pallor (pale appearance to the skin), cyanosis (bluish discoloration) or cold and clammy skin, 5) severe or unusual shortness of breath, 6) central nervous system symptoms, including ataxia, vertigo, visual or gait problems, and/or confusion, 7) irregular pulse, 8) extreme fatigue, 9) skeletal fracture, and/or 10) patient's request to stop. Relative indications include: 1) increasing chest pain, 2) physical or verbal manifestations of shortness of breath or severe fatigue, 3), wheezing, 4) leg cramps or intermittent claudication (grade 3 on a 4-point scale), and/or 5) hypertensive response.

6.2.1.2.2 Reporting and Recording Adverse Events

All AEs and serious AE(SAE)s reported by the patient, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means will be immediately recorded in the patient's medical record and on the AE form. All AEs will be reviewed by the principal investigator. The investigator is responsible for notifying the HREBA-CC about AEs.

6.2.1.2.3 Follow up of Adverse Events

Return to exercise following reporting of an adverse event which requires updated physician clearance will be discussed on a case by case basis. 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 supervising the exercise program will modify the program accordingly at re-introduction. If no physician clearance is deemed necessary the participant can return to training upon clearance from the exercise physiologist.

6.2.1.2.4 Analysis of Safety and 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 summarized 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.

6.3 Auditing

Given that this trial is a single site study of an exercise intervention, no auditing/monitoring independent from the investigators is planned.

7 Approvals

7.1 Ethics

We ensure that the ERASE Trial will be submitted to the HREBA-CC for the study protocol, informed consent form, and any informational materials given to the patient or used to recruit patients.

7.1.1 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The HREBA-CC must approve the protocol, informed consent form and any trial materials given to participants.

7.1.2 Subject Identification

A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all CRFs.

7.2 Operational Approvals

This study will be conducted at the Behavioral Medicine Laboratory (BML), the Behavioral Medicine Exercise Testing Facility (BMET), BMFC, the NAUC, and the immune assay lab. The principal investigator, Dr. Courneya, directs BML, BMET, and BMFC, which no further operational approvals will be necessary. The operational approvals have been obtained for the NAUC via the co-investigator, Dr. Adrian Fairey, and the GU Tumour Board and for the biochemical assay lab via its director and the co-investigator, Dr. Catherine Field.

8 Protocol Amendments

All amendments to the protocol (e.g., changes to eligibility criteria, outcomes, and analyses) must undergo review by the HREBA-CC. Amendments will be circulated to all participating investigators in a standard format with clear instructions regarding the HREBA-CC review.

9 Protocol Registration

The information regarding this trial has been made publicly available on the internet at www.clinicaltrials.gov with the trial registration number of NCT03203460.

10 Publication Policy

The publication of the main trial results will be written by the Principal Investigator on the basis of the final analysis and will be sent to a major scientific journal. Authors of the manuscript will include at least the Principal Investigator and any co-investigators who have i) included eligible patients in the trial (by order of inclusion) or ii) contributed significantly to the design, conduct and data interpretation regarding companion basic science studies.

Publication or presentation of study data before the publication of the primary trial endpoint may be authorized at the discretion of the Principal Investigator. The data collected during this study are confidential.

11 References

1. Canadian Cancer Society. *Canadian Cancer Statistics 2017.* 2017.
2. Talcott JA, Rieker P, Clark JA, et al. Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study. *Journal of Clinical Oncology.* 1998;16(1):275-283.
3. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *New England Journal of Medicine.* 2016;375(15):1425-1437.
4. Chen RC, Basak R, Meyer A, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA.* 2017;317(11):1141-1150.
5. Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *The lancet oncology.* 2004;5(2):101-106.
6. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. *Journal of Clinical Oncology.* 2011;29(27):3669-3676.
7. Dall'Era MA, Evans CP. The economics of active surveillance for prostate cancer. In: *Active Surveillance for Localized Prostate Cancer.* Springer; 2012:179-185.
8. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment. *Cancer.* 2012;118(14):3512-3518.
9. Lao C, Edlin R, Rouse P, et al. The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer. *BMC cancer.* 2017;17(1):529.
10. Dragomir A, Cury FL, Aprikian AG. Active surveillance for low-risk prostate cancer compared with immediate treatment: a Canadian cost comparison. *CMAJ Open.* 2014;2(2):E60-68.
11. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA.* 2015;314(1):80-82.
12. Wallace M. Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. Paper presented at: Oncology nursing forum2002.

13. Parker PA, Davis JW, Latini DM, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int.* 2016;117(3):469-477.
14. Latini DM, Hart SL, Knight SJ, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *The Journal of urology.* 2007;178(3):826-832.
15. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol.* 2005;174(3):1065-1069; discussion 1069-1070.
16. Daubenmier JJ, Weidner G, Marlin R, et al. Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. *Urology.* 2006;67(1):125-130.
17. Ornish DM, Lee KL, Fair WR, Pettengill EB, Carroll PR. Dietary trial in prostate cancer: Early experience and implications for clinical trial design. *Urology.* 2001;57(4 Suppl 1):200-201.
18. Ornish D, Lin J, Daubenmier J, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *The lancet oncology.* 2008;9(11):1048-1057.
19. Frattaroli J, Weidner G, Dnistrian AM, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology.* 2008;72(6):1319-1323.
20. Ornish D, Lin J, Chan JM, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *The Lancet Oncology.* 2013;14(11):1112-1120.
21. Eriksen AK, Hansen RD, Borre M, et al. A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials.* 2017;18(1):20.
22. Demark-Wahnefried W, Nix JW, Hunter GR, et al. Feasibility outcomes of a presurgical randomized controlled trial exploring the impact of caloric restriction and increased physical activity versus a wait-list control on tumor characteristics and circulating biomarkers in men electing prostatectomy for prostate cancer. *BMC cancer.* 2016;16(1):1.
23. Kenfield SA, Chang ST, Chan JM. Diet and lifestyle interventions in active surveillance patients with favorable-risk prostate cancer. *Current treatment options in oncology.* 2007;8(3):173-196.
24. Burton AJ, Martin RM, Donovan JL, et al. Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. *Cancer Epidemiol Biomarkers Prev.* 2012;21(10):1877-1885.
25. Vandersluis A, Guy D, Klotz L, et al. The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate cancer and prostatic diseases.* 2016.
26. Leung PS, Aronson WJ, Ngo TH, Golding LA, Barnard RJ. Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. *J Appl Physiol (1985).* 2004;96(2):450-454.

27. Jones LW, Antonelli J, Masko EM, et al. Exercise modulation of the host-tumor interaction in an orthotopic model of murine prostate cancer. *J Appl Physiol (1985).* 2012;113(2):263-272.
28. McCullough DJ, Nguyen LM, Siemann DW, Behnke BJ. Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol (1985).* 2013;115(12):1846-1854.
29. Pedersen L, Idorn M, Olofsson GH, et al. Voluntary running suppresses tumor growth through epinephrine-and IL-6-dependent NK cell mobilization and redistribution. *Cell metabolism.* 2016;23(3):554-562.
30. Jones LW, Hornsby WE, Freedland SJ, et al. Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. *European urology.* 2014;65(5):852-855.
31. Cormie P, Newton RU, Spry N, Joseph D, Taaffe DR, Galvao DA. Safety and efficacy of resistance exercise in prostate cancer patients with bone metastases. *Prostate cancer and prostatic diseases.* 2013;16(4):328-335.
32. Cormie P, Galvão DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU international.* 2015;115(2):256-266.
33. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *Journal of clinical oncology.* 2009;27(3):344-351.
34. Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *Journal of clinical oncology.* 2010;28(2):340-347.
35. Park S-W, Kim TN, Nam J-K, et al. Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology.* 2012;80(2):299-306.
36. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of clinical oncology.* 2003;21(9):1653-1659.
37. Uth J, Hornstrup T, Schmidt JF, et al. Football training improves lean body mass in men with prostate cancer undergoing androgen deprivation therapy. *Scandinavian journal of medicine & science in sports.* 2014;24(S1):105-112.
38. Farris MS, Kopciuk KA, Courneya KS, McGregor SE, Wang Q, Friedenreich CM. Identification and prediction of health-related quality of life trajectories after a prostate cancer diagnosis. *Int J Cancer.* 2017;140(7):1517-1527.
39. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *The Journal of urology.* 2005;174(3):1065-1070.

40. Li C, Carli F, Lee L, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical endoscopy.* 2013;27(4):1072-1082.
41. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *American Journal of Physical Medicine & Rehabilitation.* 2013;92(8):715-727.
42. Hayes BD, Brady L, Pollak M, Finn SP. Exercise and prostate cancer: evidence and proposed mechanisms for disease modification. *Cancer Epidemiology and Prevention Biomarkers.* 2016;25(9):1281-1288.
43. Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and mechanisms of aerobic exercise on cancer initiation, progression, and metastasis: a critical systematic review of in vivo preclinical data. *Cancer research.* 2016.
44. Ruiz-Casado A, Martin-Ruiz A, Perez LM, Provencio M, Fiuza-Luces C, Lucia A. Exercise and the Hallmarks of Cancer. *Trends Cancer.* 2017;3(6):423-441.
45. Idorn M, Hojman P. Exercise-dependent regulation of NK cells in cancer protection. *Trends in molecular medicine.* 2016;22(7):565-577.
46. Idorn M, thor Straten P. Exercise: A new role for an old tool. *Molecular & cellular oncology.* 2016;3(4):e1163005.
47. Simpson RJ, Bigley AB, Agha N, Hanley PJ, Bollard CM. Mobilizing Immune Cells With Exercise for Cancer Immunotherapy. *Exercise and Sport Sciences Reviews.* 2017;45(3):163-172.
48. Bigley AB, Simpson RJ. NK cells and exercise: implications for cancer immunotherapy and survivorship. *Discovery medicine.* 2015;19(107):433-445.
49. Ngo TH, Barnard RJ, Leung P-S, Cohen P, Aronson WJ. Insulin-like growth factor I (IGF-I) and IGF binding protein-1 modulate prostate cancer cell growth and apoptosis: possible mediators for the effects of diet and exercise on cancer cell survival. *Endocrinology.* 2003;144(6):2319-2324.
50. Gennigens C, Menetrier-Caux C, Droz J. Insulin-Like Growth Factor (IGF) family and prostate cancer. *Critical reviews in oncology/hematology.* 2006;58(2):124-145.
51. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature reviews Immunology.* 2011;11(9):607.
52. Helgerud J, Hoydal K, Wang E, et al. Aerobic High-Intensity Intervals Improve VO_{2max} More Than Moderate Training. *Medicine and science in sports and exercise.* 2007;39(4):665.
53. Gibala MJ, Little JP, MacDonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology.* 2012;590(5):1077-1084.
54. Poole DC, Gaesser GA. Response of ventilatory and lactate thresholds to continuous and interval training. *Journal of Applied Physiology.* 1985;58(4):1115-1121.

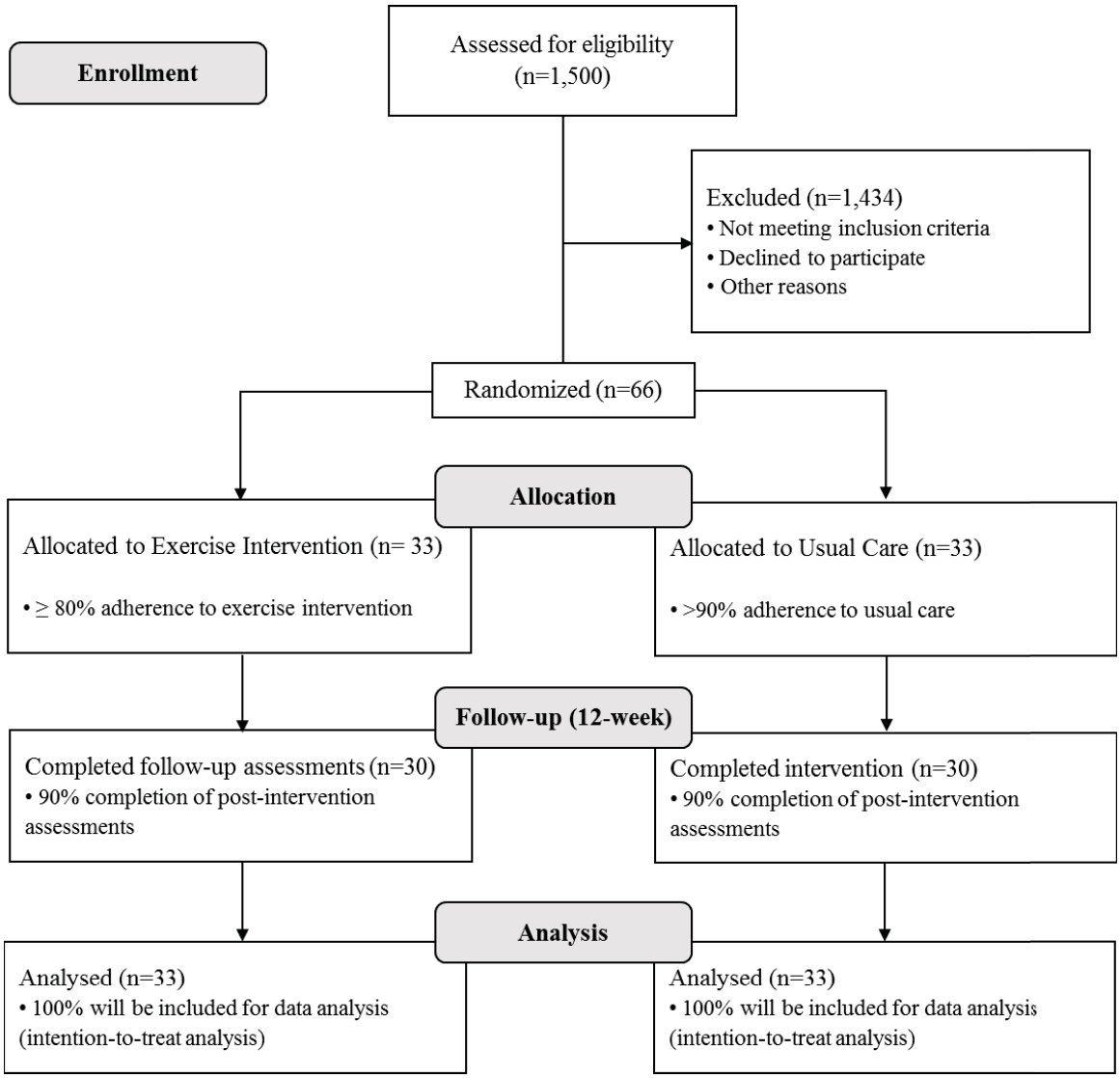
55. Warburton DE, McKenzie DC, Haykowsky MJ, et al. Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American journal of cardiology.* 2005;95(9):1080-1084.
56. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *American heart journal.* 2009;158(6):1031-1037.
57. Licker M, Karenovics W, Diaper J, et al. Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: a randomized controlled trial. *Journal of Thoracic Oncology.* 2016.
58. Schmitt J, Lindner N, Reuss-Borst M, Holmberg HC, Sperlich B. A 3-week multimodal intervention involving high-intensity interval training in female cancer survivors: a randomized controlled trial. *Physiol Rep.* 2016;4(3).
59. Toohey K, Pumpa KL, Arnolda L, et al. A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. *PeerJ.* 2016;4:e2613.
60. Devin JL, Sax AT, Hughes GI, et al. The influence of high-intensity compared with moderate-intensity exercise training on cardiorespiratory fitness and body composition in colorectal cancer survivors: a randomised controlled trial. *Journal of cancer survivorship.* 2016;10(3):467-479.
61. Sasso JP, Eves ND, Christensen JF, Koelwyn GJ, Scott J, Jones LW. A framework for prescription in exercise-oncology research. *Journal of cachexia, sarcopenia and muscle.* 2015;6(2):115-124.
62. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol.* 2007;60(12):1234-1238.
63. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *Jama.* 2009;301(19):2024-2035.
64. Norris MK, Bell G, North S, Courneya K. Effects of resistance training frequency on physical functioning and quality of life in prostate cancer survivors: a pilot randomized controlled trial. *Prostate cancer and prostatic diseases.* 2015;18(3):281-287.
65. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *Journal of clinical oncology.* 2003;21(9):1660-1668.
66. Courneya KS, Sellar CM, Stevinson C, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. *Journal of Clinical Oncology.* 2009;27(27):4605-4612.
67. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *Journal of Clinical Oncology.* 2007;25(28):4396-4404.

68. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* 1998;16(1):139-144.
69. Adams SC, DeLorey DS, Davenport MH, et al. Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. *Cancer.* 2017.
70. Borg G. *Borg's perceived exertion and pain scales.* Human kinetics; 1998.
71. Godin G, Shephard R. Godin leisure-time exercise questionnaire. *Med Sci Sports Exerc.* 1997;29(6):36-38.
72. Scott JM, Hornsby WE, Lane A, Kenjale AA, Eves ND, Jones LW. Reliability of maximal cardiopulmonary exercise testing in men with prostate cancer. *Medicine and science in sports and exercise.* 2015;47(1):27.
73. Richard C, Wadowski M, Goruk S, Cameron L, Sharma AM, Field CJ. Individuals with obesity and type 2 diabetes have additional immune dysfunction compared with obese individuals who are metabolically healthy. *BMJ Open Diabetes Research and Care.* 2017;5(1):e000379.
74. Mata MM, Mahmood F, Sowell RT, Baum LL. Effects of cryopreservation on effector cells for antibody dependent cell-mediated cytotoxicity (ADCC) and natural killer (NK) cell activity in 51 Cr-release and CD107a assays. *Journal of immunological methods.* 2014;406:1-9.
75. Custers JA, van den Berg SW, van Laarhoven HW, Bleiker EM, Gielissen MF, Prins JB. The cancer worry scale: detecting fear of recurrence in breast cancer survivors. *Cancer nursing.* 2014;37(1):E44-E50.
76. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. *Supportive care in cancer.* 2009;17(3):241-251.
77. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the national cancer institute.* 1993;85(5):365-376.
78. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology.* 2000;56(6):899-905.
79. Spielberger CD. *State-Trait anxiety inventory.* Wiley Online Library; 2010.
80. Roth AJ, Rosenfeld B, Kornblith AB, et al. The memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men with with prostate cancer. *Cancer.* 2003;97(11):2910-2918.
81. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychology and aging.* 1997;12(2):277.
82. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of pain and symptom management.* 1997;13(2):63-74.

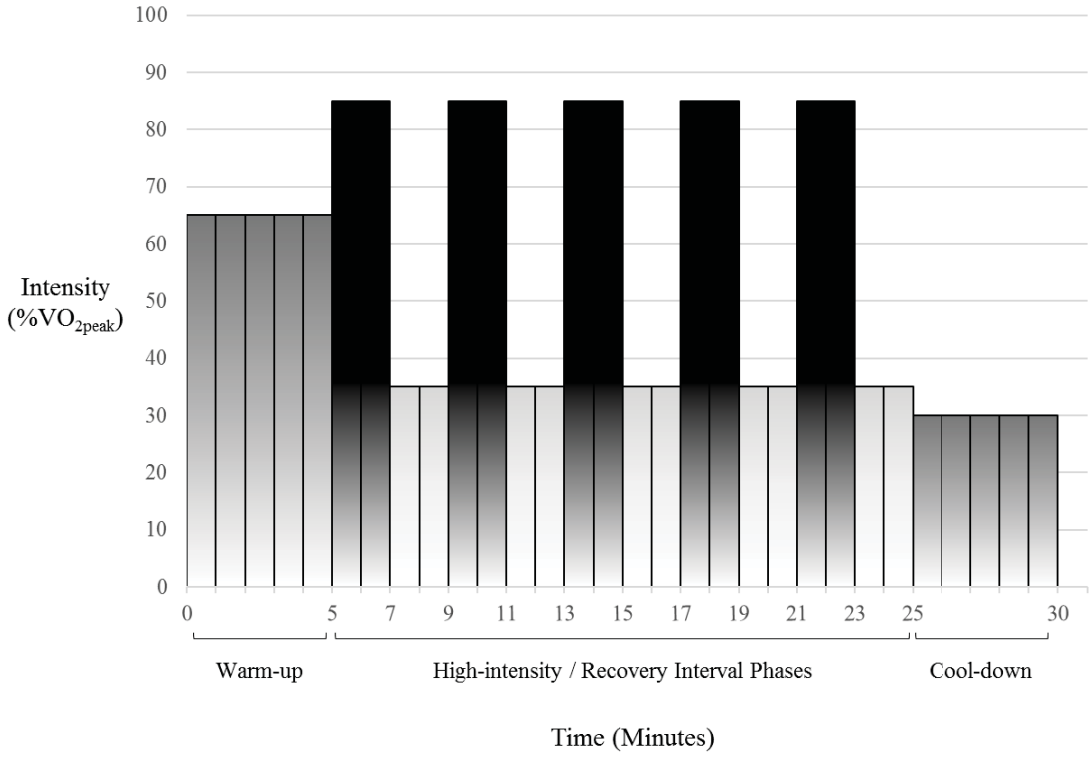
83. Cohen S, Kamarck T, Mermelstein R. Perceived stress scale. *Measuring stress: A guide for health and social scientists.* 1994.
84. Rosenberg M. Rosenberg self-esteem scale (RSE). *Acceptance and commitment therapy Measures package.* 1965;61:52.
85. Ajzen I. The theory of planned behavior. *Organizational behavior and human decision processes.* 1991;50(2):179-211.
86. Rikli RE, Jones CJ. *Senior fitness test manual.* Human Kinetics; 2013.
87. Royston P. Multiple imputation of missing values. *Stata journal.* 2004;4(3):227-241.

12 Appendices

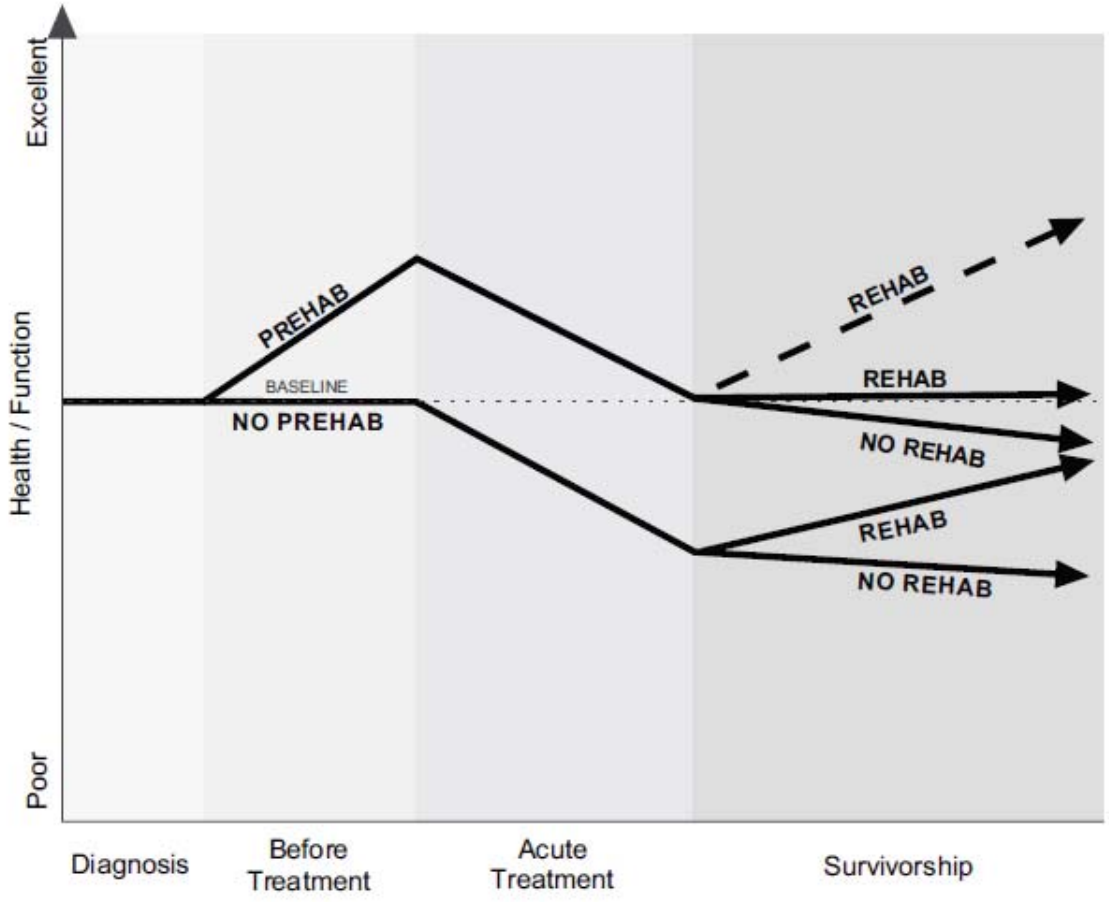
12.1 Appendix – Figure 2. Proposed flow diagram of the ERASE Trial



12.2 Appendix – Figure 3. High-intensity interval training (HIIT) Exercise Program in the ERASE trial.



12.3 Appendix – Figure4. Potential benefits of prehabilitation across cancer experience



12.4 Appendix – List of Abbreviations

Abbreviation	**Full Name**
AS	active surveillance
BMET	behavioral medicine exercise testing facility
BMFC	behavioral medicine fitness centre
CCI	cross cancer institute
CRF	cardiorespiratory fitness
CRF	case report form
HIIT	high-intensity interval training
HR	heart rate
HREBA-CC	health research ethics board of alberta-cancer committee
MET	metabolic equivalent task
MP-MRI	endo-rectal multiparametric magnetic resonance imaging
NAUC	northern alberta urology centre
PBMC	peripheral blood mononuclear cells
PCa	prostate cancer
PSA	prostate-specific antigen
(S)AE	(serious) adverse event
VO2peak	peak oxygen consumption

12.5 Appendix – Biological Specimens

Fasting blood will be taken in the morning following an overnight fast where there was no food intake after 8pm and a minimum of 48 hours since the last vigorous exercise session. Blood draws can occur on the same day as the exercise assessment, prior to the commencement of the assessments. Gloves must be worn at all times when handling specimens. Tubes, needles, and pipets must be properly disposed of in biohazard containers, in accordance with institutional requirements. A vacutainer and a 23 Gauge needle is recommended for collection. Freezers need to have an alarm monitoring system and a backup generator or other emergency system in place.

Samples will be stored in our -80○C monitored and alarmed freezer that only the research team will have access to it. Security codes are needed to get into the hall and then another set of security codes are needed to get into the room where the freezer is. A Gatekeeper Security System NU-1540 has been installed on the freezer. The Gatekeeper is an electronic keypad lock with a motor driven latch. The built-in, non-volatile memory stores an audit trail. The freezer is located in the Li Ka Shing building at the University of Alberta.

Anticipated uses of collected specimen:

- Collection of sample for immediate use: local analysis of prostate cancer-specific antigen, lipid profile, fasting glucose, HbA1c, CBCD, natural killer cell assay, proinflammatory cytokines.
- Collection of sample for banking (future use): Blood collected at baseline and post-intervention for banking.
- Analysis of banked samples: Baseline and post-intervention samples will be used for the analysis from the banked centres.

Specimens will be used to determine whether biomarkers of inflammation, energy metabolism, and androgen metabolism are associated with tumour progression among prostate cancer patients undergoing active surveillance, and explore the extent to which these biomarkers mediate the hypothesized association between high-intensity interval training and tumour progression.