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Impact of a home-based exercise program on prognostic biomarkers in men with prostate cancer

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PROTOCOL V. 1.0

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INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol CTRC# 15-0008 and will adhere to the study requirements as presented, including all statements regarding confidentially. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Clinical Investigator: _____

Institution: _____

_____ _____

Investigator Signature Date

ABBREVIATIONS

AE	Adverse Event
CTRC	Cancer Therapy and Research Center
DSM	Data Safety Monitoring
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
DSO	Data and Safety Officer
DQA	Director of Quality Assurance
EPCA	Early prostate cancer antigen
IRB	Institutional Review Board
QAD	Quality Assurance Division
PALS	Priority of Audit Level Score
PCa	Prostate Cancer
PI	Principal Investigator
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
SAE	Serious Adverse Event
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others
uPA	Urokinase plasminogen activator
uPAR	Urokinase plasminogen activator receptor
UTHSCSA	University of Texas Health Science Center at San Antonio

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1.0 INTRODUCTION AND RATIONALE

Several reports suggest that physical activity after cancer diagnosis is associated with better cancer-specific and overall survival in individuals diagnosed with PCa.[1,2] The role of a healthy diet and sufficient physical activity in cancer prevention have been well documented,[3,4] and it is widely accepted that a lack of exercise can increase an individual's risk of recurrence or developing new cancers. Increasing attention is now being given to the role of lifestyle in cancer survivorship. There is a growing body of evidence for lifestyle interventions that aim to promote physical activity as having the potential to counter some of the adverse effects of cancer treatments, disease progression and other health outcomes.[5] Exercise performed 2-3 times a week has been shown to improve physical fitness, functional performance, and quality of life in men with PCa;[1,2,6-11] however, few men with PCa exercise regularly and do not meet national physical activity guidelines.[9,12,13] A potential explanation on the lack of exercise in men with PCa is the absence of a structured, home-based, exercise program. While studies have shown positive effects of exercise in men with PCa,[1,6,11,14,15] little is known about how physical activity effects tumor physiology in men with PCa. The primary objective of this pilot study is to gather preliminary data regarding the impact of a novel, home-based exercise program on PCa biomarkers associated with recurrence and metastasis of PCa in men under active surveillance.

1.1 Prognostic Biomarkers for PCa Recurrence. Over the years, many biomarkers have been used for the diagnosis and follow-up of PCa. **PSA (**prostate specific antigen) is the most common marker used, however, recently PSA screening has fallen under controversy based on the high number of false positive diagnosis for PCa. Out of men that display elevated PSA levels in blood, only 25% are associated with PCa.[16] Therefore, other biomarkers need to be studied to more accurately determine the impact of exercise on disease progression. PSMA, EPCA, uPA and uPAR are promising PCa markers shed by the tumor that represent the advancement or regression of the prostate tumor that can be quantified in blood. Prostate-specific membrane antigen (**PSMA)** is a type II integral membrane glycoprotein that is overexpressed in the epithelial cells of PCa patients.[17] Literature supports its role in measuring progression of PCa post treatment based on its 94.5% specificity to PCa from other types of malignancy.[17] Early prostate cancer antigen (**EPCA)** is a prostate cancer-associated nuclear structural protein displaying sensitivity and specificity for prostate cancer. In a recent study, EPCA was been found to be significantly elevated in localized PCa and strongly predicted cancer progression.[18] Urokinase plasminogen activator (**uPA**) and its receptor (**uPAR**) have been connected with PCa stage and bone metastases.[19] Preoperative plasma uPA was a strong predictor of biochemical recurrence.[20] Elevated levels of both preoperative uPA and uPAR were associated with aggressive biochemical recurrence including development of distant metastasis, suggesting an association with occult metastatic disease.[20] The uPA axis is involved in various phases of tumor development and can be used as a biomarker to determine the effectiveness of exercise in modulating tumor progression.[21] Circulating tumor cells (CTCs) can be quantified through microfiltration and as indicative of advanced prostate cancer and can be an alternative source for disease profiling and

prognostication.[22] While tumor biopsies following an exercise intervention fall outside the scope of current practices in PCa treatment, these biomarkers have the potential to act as circulating biopsy of the tumor.

1.2 Biomarker for Cancer-related Fatigue. Prostate cancer survivors commonly report having 1 or more cancer related symptom that impacts their quality of life. One common symptom associated with cancer, termed cancer-related fatigue, is exceedingly common and treatable not only in prostate cancer patients but other cancers as well.[23] Cancer-related fatigue is reported by 50-90% of patients as a symptom of their cancer [4].[24] Patients report fatigue as one of the most important and distressing symptoms related to cancer and its treatment and is a strong predictor of clinical patient satisfaction as well as patient quality of life. Measurement of fatigue in PCa has typically come in the form of paper-based surveys Opportunities exist for advancing the field with novel methods of assessing fatigue in this clinical population. Biomarkers would provide an objective method to track a patient's fatigue level during treatment, allowing clinicians to optimize treatment with respect to the patient's fatigue level. In previous studies, our collaborators at Hyperion Biotechnology identified a salivary biomarker of physical fatigue, called the Fatigue Biomarker Index (FBI)[25] and demonstrated the utility of this marker in predicting the outcome of physically demanding military training.[26] Using a similar approach to biomarker discovery, the same collaborators have also identified a salivary biomarker candidate for chronic fatigue syndrome.[27] Both of these salivary biomarkers are based on changes in levels of naturally occurring peptide fragments arising from the same family of salivary proteins, the salivary Proline –rich Proteins (PRPs). Others have also identified changes in the levels of similar salivary peptides in Sjogren's syndrome, a disease associated with significant fatigue.[28] Taken together, these finds suggest a fundamental physiological link between a person's fatigue level and the composition of the individual's saliva. Investigating whether similar changes in saliva are associated with fatigue is justified.

1.3 Survey measurements for quality of life. Quality of life will be measured using the Short-Form-36 and the Functional Assessment of Chronic Illness Therapy-Fatigue surveys.

Health-Related Quality of Life (SF-36) is designed to assess the health status of patients and has been used previously in this population [29]. The SF-36 assesses eight components of quality of life (physical functioning, role functioning, bodily pain, general health, vitality, social functioning, mental health, and emotional health) that is evidence generated with well-established reliability and validity to support its use.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a self-reported survey evaluating the impact of fatigue in the patient population. The FACIT-F is a 13 item survey rated on a 5 point scale deemed reliable and valid in measuring fatigue.

1.4 Rationale for this trial design. This first of its kind study intends to collect preliminary data on the impact of a home-based exercise program that can improve prognosis, physical function and quality of life in men with PCa; the results of which have the potential to promote health restoration and wellness while reducing cancer

progression in men with PCa. This study will provide data on the feasibility in conducting a home based exercise study and pilot data on the impact of exercise on circulating concentrations of biomarkers reported in the literature to be beneficial for the prognostication of prostate cancer and salivary biomarker for fatigue.

2.0 STUDY OBJECTIVES

2.1 Primary Objective: To demonstrate the impact of a home based exercise program versus wait-list control to modulate circulating prognostic biomarkers PSA, PSMA, EPCA, uPA and uPAR in men with prostate cancer under active surveillance..

2.1.1 Hypothesis: The home based exercise program participants will have significantly lower concentrations of circulating biomarkers compared to their non-exercising counterparts.

2.2 Secondary Objective: To determine the impact of a home based exercise program versus wait-list control to modulate a novel salivary biomarker for fatigue in men with prostate cancer under active surveillance.

2.3 Other Objective:

2.3.1 To demonstrate the capability of a home based exercise program versus wait-list control in improving physical function (as measured by the 6 minute walk) and body composition in men with prostate cancer under active surveillance.

2.3.1.1 Hypothesis: The exercise group will have significant improvements in the physical function measure and body composition compared to the wait-list control group

2.3.2 To demonstrate the feasibility of conducting a home based exercise investigation.

2.3.2.1 Hypothesis: Based on the simplicity of this program, we believe that we will be able to achieve our desired recruitment and retention needs to complete the objectives of this study.

3.0 STUDY DESIGN

3.1 Description of the protocol

This study is designed randomized controlled, 2 arm parallel group pilot study.

3.2 Duration of study participation

The estimated study duration for each participant in this study is 24 week. The duration of the protocol was selected based on recommendation from the American College of Sports Medicine's Guide to Exercise and Cancer Survivorship for aerobic exercise prescription.[30]

3.3 Interim analysis

Interim analysis will be performed once all participants have completed the 12th week of the project. This analysis will be done on the efficacy and safety of the intervention. We will do a between group comparison of circulating biomarkers and a review of adverse events (see section 8.1 for full analysis plan).

4.0 SELECTION OF PATIENT

4.1 Number of patients planned

This study plans to enroll 30 men with prostate cancer under active surveillance with 15 men in each arm.

4.2 Inclusion criteria

- men aged 40 years or older
- diagnosed with prostate cancer
- under active surveillance
- Subjects willing and able to provide consent to participating in the study.

4.3 Exclusion criteria

- severe cardiac disease (New York Heart Association class III or greater)
- angina
- severe osteoporosis
- uncontrolled hypertension (blood pressure > 160/95mm Hg)
- uncontrolled sinus tachycardia (> 120 beats per minute)
- uncontrolled congestive heart failure third-degree atrio-ventricular heart block, active pericarditis or myocarditis, recent embolism, thrombophlebitis, deep vein thrombosis, resting ST displacement (> 3mm), uncontrolled diabetes, uncontrolled pain, cognitive impairment, history of falls due to balance impairment or lost of consciousness,
- severe neuromusculoskeletal conditions that limit their ability to perform walking exercise (including ataxia, peripheral or sensory neuropathy, unstable bone lesion, severe arthritis, lower limb fractures within 6 months, lower limb amputation).

5.0 DESCRIPTION OF INTERVENTION

5.1 Home-based exercise program. The intervention will include a combination of both aerobic and body-weight based exercises. The aerobic portion of the intervention will include 5 days of light to moderate intensity walking for 30 mins (weekly total of 150 mins). Intensity will be set at 40-60% of the individual's heart rate reserve using the Karvonen formula (Exercise HR = % of target intensity (HR_{max} – HR_{rest}) + HR_{rest}). Participants

will be given their targeted HR range by the PI and will be taught how to palpate and calculate HR prior to the beginning of the program. The body-weight based exercises will be done 3 times a week. Exercises will consist of 3 sets of 15 reps of bodyweight squats, incline push-ups, and hip thrusts. If these exercises cannot be performed, lower intensity exercises such as sit-to-stand, wall push up and pelvic tilt can be replaced. These exercises are aimed at increasing strength and endurance of the major muscle groups of the body. Individuals in this group will be given a pocket guide with instructions on how to safely perform the exercises and document the completion of the exercises.

5.2 Waitlist-Control Group. Participants assigned to this group will be asked to maintain normal activity and visit the CTRC fitness center for research appointments.

5.3 Method of assigning patients to intervention group. Patients eligible to participate in this study will be allocated to either the exercise group or wait-list control group (1:1) based on a pre-specified randomization list

Example:
Set #1: 2, 1, 2, 2, 1, 2, 2, 2, 1, 1, 2, 2, 2, 1, 2, 1, 2, 2, 2, 1, 1, 1, 1, 2, 2, 1, 2, 1, 2, 2
1: Control Group; 2: Intervention Group

6.0 HANDLING OF PATIENT WITHDRAWAL

Patients may withdraw from the study at any time during the study. Patients may also be withdrawn from the study for not following study related procedures or for the benefit of the patient as determined by study investigators. In the event that a patient withdraws from the study or withdrawn from the study, every attempt should be made to complete the final visit of the study (visit 4 from below). The reason for study discontinuation will be recorded in the subject's folder and case report forms.

All attempts will be made to keep participants in this study. Based on the feasibility aim of this study, the non-compliance guidelines are very lenient. Patients will be withdrawn for non-compliance if they meet any combination of the following: inactivity for 3 consecutive weeks; and/or missing 2 consecutive study appointments where outcome variables are collected.

Patients who discontinue study participation will not be replaced.

In the case study discontinuation is due to an adverse event, such patients will be closely monitored until the resolution or stabilization of this adverse event. This may mean that follow-up will continue after the patient has completed the end of study procedures. Although data on that adverse event will continue to be captured, even beyond the last visit, only those that occur up through the last visit will be recorded.

7.0 STUDY PROCEDURES

7.1 Visit schedule

Patients will be asked to attend 4 visit with the study investigators. Description of each visit is detailed below.

7.2 Pre-screening procedures

Study subjects will be recruited from patients population treated at the University of Texas Health Science Center at San Antonio's Medical Arts and Research Center Urology Clinic. Medical records will be reviewed to determine eligibility. Eligible participants will be mailed recruitment materials and asked to call the investigators if interested in participating in the study. Also, eligible participants will also be approached during regularly scheduled clinic appointments and introduced to the study. Only interested participants will be enrolled into the study.

7.3 Description by type of visit

7.3.1 Visit 1 (Baseline Visit) – This will be the first visit in this study and should last about 30-45 minutes. At this session, we will review the consent form, explain the purpose and procedures of the study, ask the subject to sign the consent form if you agree to participate in the study, and randomly assign the subject to one of the two groups mentioned above. Following this, the following things will happen:

1. Assignment of a Nike FitBit – Each participant, no matter which study arm, will be provided with a Nike Fitbit during the 6 month program. The FitBit will monitor activity and will assist the research team in tracking activity and sleep habits. We will instruct subjects on the use and care of the FitBit.

2. Blood Draw –15 mL of blood (two tubes or 1 tablespoon or 3 teaspoons) to measure circulating markers (PSA, PSMA, EPCA, uPA and uPAR) and circulating tumor cells.

3. Saliva Collection – we will collect about 4 mL of saliva (1/4 of a tablespoon or ¾ teaspoon) to measure FBI concentrations in saliva.

4. Surveys for Quality of Life and Fatigue – subjects will be asked to complete 2 surveys that will take about 5 minutes to complete. These surveys are:
    a. Health-Related Quality of Life (SF-36) – this survey will assess subject's overall health status, including physical functioning, role functioning, bodily pain, general health, vitality, social functioning, mental health and emotional health.
    b. Functional Assessment of Chronic Illness – Fatigue (FACIT-F) – This survey evaluates the impact of fatigue in men with prostate cancer.

5. Body Composition, Body Mass Index and Body Density – will measure body fat percentage by measuring skinfold thickness at 3 sites (chest, abdomen, thigh). Body density will be measured using body fat percentage plus the addition of waist and arm circumference. Body mass index will be calculated by collecting by height and weight measurements from the subjects.

6. 6 minute walk test –overall physical function will be measured using the 6 minute walk test. We will track the distance traveled and use this as baseline score.

7.3.2 Visit 2 and Visit 3 (12 week and 18 week visit) – the following activities will be done at the 12 week and 18 week visit:

1. Blood Draw – we will collect 10 mL (2 teaspoons) to measure circulating markers (PSA, PSMA, EPCA, uPA and uPAR). Note: This is different than at baseline and final visit to quantify circulating tumor cells.

2. Download FitBit Data – subjects will be asked to bring the FitBit to this visit so we can download the data that is on the FitBit.

3. Saliva Collection – we will collect about 4 mL of saliva (1/4 of a tablespoon or ¾ teaspoon) to measure FBI concentrations in saliva

4. Body Composition, Body Mass Index and Body Density – will measure body fat percentage by measuring skinfold thickness at 3 sites (chest, abdomen, thigh). We will also measure body mass index by collecting height and weight. Body density will be measured using body fat percentage plus the addition of waist and arm circumference.

7.3.3 Visit 4 (24 week visit; End of Study Visit) – the following activities will be done at the 24 weeks visit (or end of study visit)

1. Blood Draw – we will collect 15 mL of blood (two tubes or 1 tablespoon or 3 teaspoons) to measure circulating markers (PSA, PSMA, EPCA, uPA and uPAR) and circulating tumor cells.

2. Saliva Collection – we will collect about 4 mL of saliva (1/4 of a tablespoon or ¾ teaspoon) to measure FBI concentrations in saliva

3. Surveys for Quality of Life and Fatigue – subjects will be asked to complete 2 surveys that will take about 5 minutes to complete. These surveys are:

    a. Health-Related Quality of Life (SF-36) – this survey will assess subject's overall health status, including physical functioning, role functioning, bodily pain, general health, vitality, social functioning, mental health and emotional health.
    b. Functional Assessment of Chronic Illness – Fatigue (FACIT-F) – This survey evaluates the impact of fatigue in men with prostate cancer.

4. Body Composition, Body Mass Index and Body Density – will measure body fat percentage by measuring skinfold thickness at 3 sites (chest, abdomen, thigh). We will also measure body mass index by collecting height and weight. Body density will be measured using body fat percentage plus the addition of waist and arm circumference.

5. 6 minute walk test – we measure overall physical function by asking subjects to walk for 6 minutes. We will track the distance traveled and use this as the post-intervention score.

6. Return Nike FitBit – subjects will be asked to return the Nike FitBit to the research team. Data from the FitBit will be downloaded. After downloading, all data that is on the FitBit will be erased. A summary of the subject's activity can be provided if desired.

7.4 Sample Processing

7.4.1 Serum Processing

Whole blood will be collected through the antecubital vein in the non-dominant arm into a red topped vacutainer with clot activator. After inverting 3-5 times to ensure proper mixing, samples will be centrifuged at 2,000 x g for 15 minutes. Serum will be aliquoted in .5 mL samples and stored in a -80C freezer until analysis.

7.4.2 Saliva Processing

Raw saliva samples (~4 ml) will be collected by passive drooling into two 2mL tubes. Within 30 minutes of collection that sample is placed in a -80C freezer. After the completion of each time point, one 2mL tube for each participant will be transported to the Hyperion laboratory located at 12002 Warfield, San Antonio, TX and stored at -80C until analysis.

8.0 STATISTICAL CONSIDERATIONS

8.1 Statistical analysis plan

Analysis will be done after all participants have completed the 12-week and 24-week timepoints, respectively. The interim analysis at 12-weeks will be for safety and efficacy of the intervention and will include a between group comparison of circulating biomarkers and a review of adverse events reported by study participants.

Statistical analysis will be performed using IBM SPSS 19.0 software. A 2 group analysis of variance (ANOVA) will be used to compare changes in biomarkers, physical function, body composition, body density, and quality of life between the exercise group and the WLC. Pearson's Product Moment Correlation will be used to measure associations between biomarkers in Aim 1 to body composition, body density, physical function and quality of life measured in aim 2. A value of $p<0.05$ will be considered statistically significant. The results of this study will be used to calculate power and determine sample size for future research questions in this field.

We will also evaluate the projects procedures and timeline for feasibility. We will document and review our timelines for recruitment for this pilot and ask participants to comment on their experiences in this project with pointed efforts to understand ways to improve the project procedures for effectiveness and efficiency. We will also assess feasibility by documenting and reviewing study patient description described below.

8.2 Study patient description

We will assess the number of participants screened per month and the percentage of screen eligible participants that were randomized into the study. We will assess intervention adherence and participant retention. Adherence will be based on the participant's ability and willingness to perform the prescribed activities. Retention will be defined as percentage of assessments completed. The number of randomized patients will be summarized by age, ethnicity. The number of patients either completing or permanently discontinuing the exercise routine and other interventions will be summarized using counts and percentages.

8.3 Clinical Trial Protocol deviations

All the following deviations will be summarized on the all randomized patient population: • Inclusion or exclusion criteria not satisfied. • Deviations related to the interventional arm • NOTE: A one week window from the scheduled visit is allowed for all visit time periods.

8.4 Handling of dropouts or missing data

All randomized patients will be included in the primary analysis.

9.0 PATIENT SAFETY

9.1 Data Safety Monitoring Board

A Data and Safety Monitoring Plan (DSMP) is required for all an individual protocols conducted at CTRC. All protocols conducted at CTRC are covered under the auspices of the CTRC Institutional Data Safety Monitoring Plan.

The CTRC Institutional DSMP global policies provide individual trials with:

- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the CTRC Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS) ,
- oversight by the Data Safety Monitoring Committee (DSMC), and
- verification of protocol adherence via annual audit for all Investigator Initiated Studies by the CTRC Quality Assurance Division.

9.1.1 Monitoring Safety

Due to the low risk associated with participation in this protocol, The Principal Investigator will conduct independent review and report any findings to the CTRC Data Safety Monitoring Committee (DSMC) and the UTHSCSA IRB. It is not anticipated that any safety issues will arise from this study because it is an low risk interventional exercise study.

9.1.2 Reporting Requirements

As per the CTRC DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the DSMC.

9.1.3 Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at CTRC, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. **Self-audit of data will be performed by a member of a research team (i.e. Research Assistant)**. Protocol compliance, data accuracy

and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the CTRC DSMC.

9.1.4 Safety Definitions:

For this study, the following safety definitions will be applicable:

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

A. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);
B. definitely related or probably related to participation in the research; and
C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

All UPRISO's will be reported following CTRC and UTHSCSA institutional guidelines.

UTHSCSA UPRISO REPORTING REQUIREMENTS		
Type Event	**Report to**	**Timeframe**
UPIRSO - life threatening	**UTHSCSA IRB and QA Director**	**within 48 hours of the PI determining a UPIRSO exists**
UPIRSO - non-life threatening	**UTHSCSA IRB and QA Director**	**within 7 days of the PI determining a UPIRSO exists**

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