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Group Exercise Training for Fall Prevention and Functional Improvements during and after Treatment for Prostate Cancer

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Minimal-risk Protocol

Group Exercise Training for Fall prevention and functional Improvements during and after Treatment for Prostate cancer

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Protocol Revision Dates:

10/25/2018

- *Added description of participant incentives (2.0)*
- *Clarified Inclusion Criteria language regarding other treatment (5.0)*
- *Edited Exclusion Criteria language regarding exercise—made it more specific (5.0)*
- *Update language regarding OSCaR recruitment process (10.a)*

01/09/2019

- *Updated eligibility (removed aerobic exercise; clarified strength training criteria; added criteria about movement and neurological disorders)*
- *Updated randomization stratifications*
- *Added information about electronic consent*
- *Adding performance testing measures*
- *Adding questionnaires*
- *Added details about compensation and how we'll pro-rate*

02/22/2019
- Added FACIT-Fatigue to outcome measures (p. 9) and the Schedule of Events table

03/01/2019
- Added chair sit in reach to Secondary Endpoint: Physical Function (p. 10) and the Schedule of Events table

04/26/2019
- Update recruitment language to include sources such as Cohort Discovery, Research Data Warehouse, MyChart, Tuality, Adventist, etc. (section 10.a and 14.0)
- Updated eligibility inclusion/exclusion criteria (section 5.0)
- Clarified language for Adverse Event tracking and reporting (section 19.1 and 19.2)
- Updated scheduled of events for Managing Side Effects of ADT- MSQ (removed it at 3-months) (section 8.0)
- Replaced "School of Nursing" with "Knight Cancer Research Building" throughout the document

05/22/2019
- Add title to first page, per KCI audit request
- Edit Participant Incentives under section 3.0 (made the pro-rating system simpler and more inclusive)

2/5/2020
- Added further clarification and refinement of Adverse Event reporting
- Added clarification of inclusion criteria related to class attendance

4/3/2020
- 3.0 Study Design Methodology- added remote delivery of exercise classes
- 3.0 Study Design Methodology- added remote delivery of testing (and potential skipped/delayed visits)
- 7.0 Setting- Added "remote delivery" as possible setting
- 8.0 Schedule of Events- added remote testing assessments to table
- 10.0 Risks to Subjects- added remote safety considerations

5/21/2020
- 8.0 Study Procedures and Schedule of Events- Added boilerplate language for use of MyChart for recruitment
- 8.0 Study Procedures and Schedule of Events- Added 3M TUG as follow-up assessment completed during remote testing
- 7.0 Setting- Removed language related to recording classes
- 15.0 Informed consent- Added language about consent for remote delivery of study

6/9/2020

- Section 15.0 Informed consent – revising our remote e-consent process

11/17/20

- 3.0 Study Design Methodology – added Passive monitoring of functional mobility and balance (SmartSox) to Secondary Endpoint: Physical Function
- 3.0 Study Design Methodology – added Passive monitoring of functional mobility and balance (SmartSox) to list of testing measures collected during remote study visits
- 8.0 Study Procedures and Schedule of Events – added Passive monitoring of functional mobility and balance (SmartSox) to Schedule of Events

1/12/21

Added an ancillary study: Continuous passive monitoring to understand accelerated aging in prostate cancer. The following sections of the protocol were modified to include the ancillary study:

- 1.0 Background/Rationale – added additional background for ancillary study
- 2.0 Objectives – added ancillary study aim
- 3.0 Study Design/Methodology – described study design and collection of outcome measures
- 4.0 Study Population - added ancillary study participants
- 5.0 Inclusion/Exclusion Criteria – specified inclusion/exclusion criteria for ancillary study
- 8.0 Study Procedures and Schedule of Events – updated text to include ancillary study procedures
- 8.0 Study Procedures and Schedule of Events – created schedule of events for ancillary study
- 10.0 Risks to Subjects – updated to exclude ancillary study from risks due to exercise and radiation exposure
- 12.0 Timeline & Milestones – added timeline for ancillary study
- 13.0 Bio-statistical Considerations – added analysis plan for ancillary study
- 14.0 Recruitment Methods - added additional recruitment sources for ancillary study
- 20.0 Inclusion of Women, Minorities and Children – added Table 3: Projected Accrual for Ancillary Study

Added detail regarding remote delivery of the trial

- 3.0 Study Design/Methodology- added information about participant remuneration and information about additional testing visits to assess the validity of remote delivery

Added new measures

- 3.0 Study Design/Methodology – added 2 new measures: the FRAIL scale and the Cancer Loneliness Scale
- 8.0 Study Procedures and Schedule of Events – updated schedule of events to include administration of the FRAIL scale and the Cancer Loneliness Scale

2/26/2021

Added details regarding use of a daily diary for SmartSox.

3.0 Study Design/Methodology
8.0 Study Procedures and Schedule of Events

3/10/21

Added a user experience questionnaire for SmartSox

3.0 Study Design/Methodology

- 8.0 Study Procedures and Schedule of Events

5/13/21

- Removed SmartSox measurements at 3 and 12 months

    - 8.0 Study Procedures and Schedule of Events
- Added 3 meter TUG test to ancillary study
    - 3.0 Study Design/Methodology
    - 8.0 Study Procedures and Schedule of Events
- Updated 3 meter TUG test to all visits (previously remote-only)
    - 3.0 Study Design/Methodology
    - 8.0 Study Procedures and Schedule of Event
- Added Chair Sit and Reach to remote assessments (Measures & Data Collection)
    - 3.0 Study Design/Methodology

9/1/21

- Increased compensation for ancillary study
    - 3.0 Study Design/Methodology

10/28/21

- Remove Managing Side Effects of ADT Questionnaire (MSQ)
    - 3.0 Study Design Methodology
    - 8.0 Schedule of Events
- Remove Charlson Comorbidity Index from 3-month and 6-month time point
    - 8.0 Schedule of Events

04/18/2022

- Updated compensation to include hotel accommodations
    - 3.0 Study Design Methodology

07/07/2022

- Updated information about participant remuneration
    - 3.0 Study Design/Methodology
- Updated verbiage about remote setting and self-report height during remote testing
    - 3.0 Study Design/Methodology
      7.0 Setting

9/12/2024

Added ancillary study #2: Assessing physical and cognitive aging from the initiation of androgen deprivation therapy for prostate cancer. The following sections of the protocol were modified to include this ancillary study:

- 1.0 Background/Rationale – added additional background for ancillary study
- 2.0 Objectives – added ancillary study aims
- 3.0 Study Design/Methodology – described study design and outcome measures
- 4.0 Study Population - added ancillary study population
- 5.0 Inclusion/Exclusion Criteria – specified inclusion/exclusion criteria for ancillary study
- 8.0 Study Procedures and Schedule of Events – updated text to address ancillary study procedures
- 13.0 Bio-statistical Considerations – added analysis plan for ancillary study

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1.0 BACKGROUND/ RATIONALE

Two million prostate cancer survivors are alive in the U.S. and nearly half (45%) will receive androgen deprivation therapy (ADT) to reduce tumor androgen exposure and slow down cancer progression [1-3]. While beneficial for cancer survival, significant treatment-induced side effects from ADT may lead to serious health consequences including falls, frailty, and dysfunction that contribute to morbidity and mortality.[4-9]

Falls, frailty and dysfunction lead to costly injuries, loss of independence and early death among older persons. Falls are associated with 90% of hip, 50% of vertebral, and 100% of wrist fractures [10] and can cause traumatic brain injury, internal organ damage, hospitalization, disability and death [11]. One-third of those who fall will require assistance with activities of daily living and over half (58%) of those requiring help will need it for more than 6 months [12]. A single fall increases the risk of future falls [11] and recurrent falls increase the rates of nursing home admission and mortality and poor quality of life [13, 14] and may be a symptom of frailty and poor physical and mental health status [15, 16]. Frailty is an overall weakened physiological state usually associated with advanced age. Fried proposed a Frailty Phenotype model of 5 criteria to measure frailty and demonstrated that older adults with at least 3 of the 5 frailty criteria were at increased risk of hospitalization, development of disability, falls and early death [17-25]

Androgen deprivation therapy (ADT) for prostate cancer increases the risk of falls and frailty, even if treatment stops. Recent evidence, including our data, indicates that prostate cancer survivors exposed to ADT are significantly more likely to report a history of falls, injurious falls, frailty and dysfunction compared to prostate cancer survivors never on ADT [4-9]. ADT is associated with muscle loss, weakness, fatigue, slowness, and inactivity [26-28] which are linked to falls in adults without cancer, and constitute the same elements of the Frailty Phenotype that predicts poor health outcomes [29]. New findings from our team and others show that the rate of falls, including those resulting in injury, are 2-3 times higher among prostate cancer survivors who receive ADT compared to men who never receive this treatment or to otherwise healthy, older men. In addition, our data indicate that prostate cancer survivors whether treated currently or in the past with ADT, have a 5 to 6-times higher risk of recurrent falls and 9 to 10 times higher risk of frailty than men never on ADT [8]. Nearly half of all prostate cancer survivors are treated with ADT [3], placing millions of men at increased risk for these subsequently life-threatening side effects.

Currently, clinical practice has no effective solution to the rising problems of falls and frailty from ADT. Despite the high risk associated with ADT, no fall or frailty prevention strategies, especially exercise-based modalities, have been developed in this clinical population and clinical guidelines are bereft of recommendations to manage these life-threatening consequences of treatment. Exercise has been shown to offer symptomatic relief from side effects of cancer treatment and improve quality of life among cancer survivors, but the potential benefits of exercise to prevent falls and frailty associated with ADT are unknown [30]. This creates a major treatment barrier in the field of oncology care for prostate cancer survivors as both the incidence of falls and prevalence of frailty increase as a result of conventional treatment with ADT. This dilemma makes the patient-oriented clinical treatment decisions difficult for providers and prolongs patient exposure to the harmful downstream consequences of ADT. Thus, there is an urgent clinical need to identify and test non-pharmacologic, community-based fall and frailty prevention programs for this at-risk patient population.

To meet this urgent need, we propose a trial to compare the efficacy of 2 well-established, yet distinct types of exercise, tai ji quan (also known as "tai chi") vs. strength training, to prevent falls and frailty in prostate cancer survivors on ADT. Tai ji quan and strength training each reduce falls in older adults without cancer by targeting different mechanisms: balance control or muscle strength, respectively [31]. Since the precise reasons that ADT increases falls are not yet known, a rigorous head-to-head comparison of two traditional types of exercise that are grounded in the evidence from older adults without cancer must also be evaluated as a fall prevention strategy for prostate cancer survivors.

Additional background for ancillary study: A major limitation in advancing our understanding of the etiology and prevention of ADT-associated falls and frailty is that balance and gait are assessed by self-report or by laboratory-based measures. Self-report measures are prone to underestimating a problem and while performance-based measures provide an objective assessment, most people perform better in a testing environment than how they normally move in daily life. We want to go beyond understanding a patient's potential functional capacity under ideal conditions (what a patient *could do*) using supervised tests in a clinic or laboratory and understand their actual performance (what a patient *actually does*) by quantifying mobility under unsupervised conditions in daily life. Adding objective information about the quality of mobility during daily life could also improve clinicians' decision-making about who, when and how to prevent falls. Dr. Horak, a co-investigator in the parent trial, has recently developed a SmartSox system for characterizing quality and quantity of mobility in daily life. The SmartSox system is virtually unobtrusive and automatically and continuously provides objective measures of straight ahead and turning gait impairments using inertial sensors embedded into socks. Measures collected by the Smartsox include both quality of walking associated with fall risk, as well as quantity of walking activity. These metrics may be more sensitive indicators of mobility problems since they can detect decrements in gait and balance that are not picked up by traditional timed or burdensome tests in the clinic or gait laboratory. Using SmartSox wearable sensors, we may be able to discover new markers of mobility and impairment and fall risk.

Ancillary study #2:
Understanding the relationship between physical and cognitive aging is essential to reducing the harms from ADT. Evidence from both healthy older adults and adults with cognitive impairment shows that physical aging and cognitive aging are interrelated.[63] Measures of physical aging, such as slower gait speed and poorer balance,[29, 32, 63] are associated with cognitive impairment, and gait slowing in older adults with cognitive impairment is a predictor of incident dementia.[64] Similarly, in longitudinal studies of healthy older adults, gait slowing and impaired balance precede later cognitive impairment,[28-33] and gait speed is an independent predictor of cognitive decline.[65, 66] Collectively, these studies illustrate how physical and cognitive aging are interrelated and suggest that <u>similar relationships may exist between physical and cognitive aging in men with prostate cancer that are accelerated by ADT</u>.

Sensitive detection of physical and cognitive aging could lead to better strategies to promote healthy aging in men treated with ADT. Studies of physical and cognitive aging often rely on episodic administration of standard clinic-based measures, which are commonly and easily obtained on large samples of patients. However, clinic-based measures may not reflect day-to-day functioning and may lack the sensitivity and frequency of assessment needed to detect subtle changes; therefore, reliance on clinic-based measures alone limits our understanding of physical and cognitive aging. For example, prior longitudinal studies of men on ADT collected cognitive measures every 6 months with mixed success of detecting changes over time,[23-25] while a study of more frequent, monthly assessments using patient-reported

outcomes detected early and steady increases in cognitive aging over time.[12] Therefore, inclusion of sensitive, ecologically valid measures would complement data from clinic-based measures and provide a richer picture of trajectories of change in physical and cognitive aging than clinic-based measures alone. Addressing these limitations of prior work, our team has begun to study physical and cognitive aging using tools that provide both sensitive and ecologically valid data. Evaluation of physical and cognitive aging using passive sensing technology that continuously measures functioning at home could identify markers of physical and cognitive aging early on in the course of ADT. Therefore sensitive, ecologically valid measures of aging could have a major impact on clinical care for men with prostate cancer by signaling when and in whom preventative measures are needed to best guide the clinical use of ADT.

2.0 OBJECTIVES

We propose a 3-group, single-blind, parallel design randomized controlled trial in prostate cancer survivors treated with ADT to compare: 1) tai ji quan to 2) strength training and each to 3) a placebo (stretching) control group.

Our specific aims and hypotheses are:

Primary aim: To determine and compare the efficacy of tai ji quan training and strength training in reducing the incidence of falls in prostate cancer survivors on ADT.

Hypothesis: Tai ji quan and strength training groups will each reduce the incidence of falls compared to a control group. The relative efficacy of each type of training to reduce falls is not yet known.

Secondary aim*:* To determine and compare the efficacy of tai ji quan training and strength training to reduce frailty and dysfunction in prostate cancer survivors on ADT.

Hypothesis: Tai ji quan and strength training groups will each reduce the prevalence of frailty and improve physical function compared to a control group. The relative efficacy of each type of training to reduce frailty and improve physical function is not yet known.

Tertiary aim: To determine how well the benefits of Tai ji quan and strength interventions persist over a 6-month period.

Hypothesis: Group differences in the primary outcome of falls, and secondary outcomes of frailty and physical function will remain for 6 months after the end of the supervised interventions.

Exploratory Aim: To explore the patterns and predictors of types of men (including host and treatment factors) who benefit most from tai ji quan and strength training.

Ancillary study: We have received supplemental funding to conduct an ancillary study with the following aim: Determine the relationship between mobility characteristics (gait, turning as dynamic balance) during passive monitoring of up to 7 days and ADT exposure, frailty, falls and functioning in up to 130 prostate cancer survivors.

Ancillary study #2:

Aim 1. Determine the association of cognitive aging with clinical measures of physical aging in men with prostate cancer treated with ADT.

Aim 2. Determine the association of cognitive aging with wearable sensor-derived measures of physical aging in men with prostate cancer treated with ADT.

3.0 STUDY DESIGN/METHODOLOGY

To address study aims we propose the GET FIT Prostate trial (Group Exercise Training for Fall prevention and functional Improvements during and after Treatment for Prostate cancer) - a single-blind, parallel group, randomized controlled trial comparing– 1) tai ji quan and 2) strength training against each other and vs. 3) a placebo control - over a 6-mos. supervised intervention (Aims 1 & 2) and 6-mos. follow-up (Aim 3).

Study Arms

Participants in each study group will attend supervised 1-hr classes, 3 d/wk for 6 months. Certified exercise instructor(s) with 1+ years experience training older adults will be trained by the study team to lead classes. Class size will be limited to 16 participants per class so that enough individual attention is given to participants to ensure proper form and safety. To accommodate the small class size, we will have 3 sets of classes (1 per study program) per recruitment wave. For each wave, all 3 study programs will be held at each exercise location. Each intervention minimizes reliance on expensive equipment and emphasizes simple exercises based on functional movements. It is difficult to precisely equilibrate the total volume (intensity and duration) of exercise performed between experimental groups because the nature of each modality is so different. Both will be matched as closely as possible in progression from the low to high end of the range for moderate intensity over the first 3 months of the intervention. They will remain at a constant overload for the last half of the intervention.

Strength Training: Recommendations for improving muscle strength in older adults support the use of multiple-joint exercises for 1-3 sets per exercise at a weight that can be lifted 8–12 times [32]. Our strength training intervention uses weighted vests to apply resistance during lower body exercise - an innovative and safe method to maximize the effect of exercise on lower body musculoskeletal function. The strength training program used in this study is based on training programs that improved neuromuscular function (strength, gait, and balance) and reduced fall risk factors in our prior studies in women with [33, 34] or without cancer [35, 36] and in our recently completed trials in prostate cancer survivors on ADT [37-39]. Participants wear a weighted vest while performing exercises using functional movement patterns that challenge balance by using muscle groups and movement involved in everyday activities (chair rises, 90° squats, side-to-side squats, toe raises, lunges (forward, lateral, backward, walking), multi-directional step ups). The vest has multiple small pockets that each holds a ½-lb weight, so that the intensity of the exercise can be adjusted slowly. Pockets are distributed evenly around the torso in order to add resistance in an ergonomically efficient and safe way. Weighted vests allow men to perform functional exercises without safety risks related to balance disruption that can occur with handheld barbells and dumbbells.

Tai ji quan: The protocol contains an integrated exercise routine consisting of 8 purposeful movement forms and a set of therapeutic movements. This program was vigorously evaluated in 2 trials by Li et al [40, 41], and subsequently in community settings [42] and with a clinical population [43]. Because the goal of the exercise is to assist patients in retaining postural control and stability, the protocol is specifically designed to challenge limits of stability and train gait patterns, as reflected in movements such as upright trunk positioning, displacement of body's center of mass over the weight-bearing leg, and step initiation, locomotion, and termination. The only resistance applied during tai ji quan will be the participant's own body weight. The early stage of the program (i.e., the first 12 weeks) emphasizes primarily learning and practicing single forms with multiple repetitions. The later stage focuses on performing individual forms to improve postural balance and movement locomotion and reviewing and practicing forms learned in previous sessions.

Stretching Control: Participants in the control group will attend a supervised flexibility program of the same total weekly duration as the experimental arms (e.g., 3, 60-min sessions per week). Control participants will perform a series of whole body stretching exercises, according to the ACSM guidelines for flexibility training [32], with a focus on developing and maintaining a healthy back. Stretching exercises will be performed in a seated or lying position that minimizes weight-bearing forces that might increase fitness or mobility. Many exercise trials in older adults, including ours, have used a stretching control condition and have shown no effect of this training on muscle strength [44]. Since the ACSM recommends "avoidance of inactivity" among cancer survivors to optimize quality of life [30] the increases in range of motion and sense of well-being from stretching may be viewed as a benefit for participants in this group. Men in this group will be asked to refrain from initiating new strength training or tai ji quan programs during their time in the study. Our prior exercise trial in prostate cancer survivors on ADT had a similar stretching control group and retention and compliance rates were similar as men in the strength training group [38]. In contrast, in our recent trial of partnered exercise in prostate cancer survivors and spouses, couples assigned to a usual care control group had greater attrition (25%) compared to the exercise group (0%); thus, the use of a placebo control group is an important feature of this study's retention plan.

Participants will perform all exercise sessions remotely (e.g., at home) using videoconferencing software. The necessary exercise equipment and a webcam may be provided if needed, and will be returned at the end of study. Participants will receive written and verbal instructions for installing and using videoconferencing software. During these web-based, group video conferences, the exercise instructors will observe and instruct participants using the same format as on-site classes.

Quality control of intervention delivery

Delivery of 3 exercise programs at multiple sites introduces the potential for inconsistent delivery of study programs. We have taken the following steps to improve quality control over intervention delivery: 1) Exercise instructor training sessions for all instructors. A 2-day training workshop, led by Dr. Winters-Stone, Dr. Li, and the Project Director or the head exercise trainer, will cover how to instruct each exercise protocol, training progression, safety considerations, and research conduct specific to the exercise program. 2) Written guidelines will be provided for each instructor, in addition to hands-on training, that outlines the training protocols and overall study conduct to optimize delivery of the classes in a consistent fashion, 3) Rigorous oversight of class instruction. A primary role of the Project Director or the head exercise trainer will be to oversee proper conduct of exercise classes, participant retention and exercise compliance. She will observe classes on a weekly basis over the first 3 months and monthly thereafter. She or the head exercise trainer will work with instructors to minimize instructional differences across sites. Using this approach in our current fall prevention trial we have trained 7 instructors to deliver 15 study programs and have no differences across instructors on participant adherence or retention.

Participant safety during exercise

Any form of exercise carries a slight risk of injury. We have had no drop out from a study due to injury during training; however, as with any study in older adults, compliance has been affected by minor musculoskeletal complaints usually stemming from pre-existing orthopedic conditions. We take steps to reduce the risk of injury and other issues that might limit compliance, including: 1) required physician clearance for every enrolled participant and 2) monitoring and early care of musculoskeletal symptoms which may include slight adjustments in the training program (modifying intensity or select exercises) with a goal to maintain the overall training stimulus.

Six-Month Follow-Up Period

To evaluate the persistent effects of tai ji quan and strength training on falls and frailty, men will be followed for an additional 6 months after the 6-month supervised intervention stops. Men will continue to track their falls during the follow-up period using the same monthly reports employed in the intervention phase. A quarterly falls questionnaire will also be administered (3-months, 6-months, 9-months, and 12-months).We recognize that men may wish to maintain their exercise habits after formal training stops and we will not discourage them from doing so. During the follow-up period, exercise questionnaires will be used to track participation in home or community exercise programs and will be collected at the 9- and 12-month time periods. We will consider participation in community and/or home-based exercise in analysis for Aim 3 (see **Analysis Plan**) and will also repeat measures of frailty and function in order to better assess both the residual effects of the intervention programs among men who do not exercise in the follow-up period and the influence of continued exercise on outcomes after formal training stops.

Participant Incentives: To improve motivation to exercise and promote compliance to the study interventions, an incentive will be provided to participants at the mid-point and end of the intervention period. Participants will be provided with a potential to earn $50 at each 3-month time point ($100 for 6-month intervention) depending on their attendance at weekly exercise sessions. The amount received will depend on the average number of exercise class sessions attended per week. We will use the following compensation structure:

# of classes attended/12 week increment	average # of classes/week	Compensation amount
25-36	2.1-3.0	$50.00
13-24	1.1-2.0	$40.00
7-12	0.51-1.0	$30.00
0-6	0.0-0.50	$0.00

In addition there will be a $15 remuneration per in-person testing visit to offset transportation costs. There will be an additional $10 for completion of remote testing visits and $10 for the completion of surveys at each of the four main time points. Participants who complete both in-person and remote testing and complete surveys at each of the four time points will be given a maximum amount of remuneration of $140 ($35 per time point). If a participant's travel exceeds a 60-mile roundtrip, they will receive an additional $25 remuneration plus added compensation for excess miles driven (outside of the 60-mile roundtrip) using the 2020 standard mileage rate for medical visits of 17 cents per mile. This compensation will not exceed $50 per testing time point for a maximum total compensation of $200 per participant for travel. When travel exceeds 150 miles roundtrip, they may be provided with one night of hotel accommodations in the OHSU vicinity.

Measures and Data Collection

Data on falls will be collected monthly while other measures will be collected at enrollment, 3- and 6-mos. (post-intervention), and 6 mos. after completion of the intervention (follow-up). A mid-study time point is included to detect early changes in frailty and function. Total time for performance testing and survey completion is ~2-2.5 hours. Men complete written surveys on a desktop or laptop computer at baseline and online for follow-up visits, unless they prefer to complete paper surveys (~5% of participants in our last intervention trial prefer paper over online). Staff reviews surveys for completeness and follows up with participants in person or by phone on missing data.

Outcome Measures

Primary Endpoint: Falls

In this study, a fall is defined as unintentionally coming to rest on the ground or at some other lower level, not as a result of a major intrinsic event (e.g., stroke or syncope) or overwhelming hazard [13]. Falls over one year prior to baseline will be ascertained to characterize the sample and check for equality of randomization. Prospective assessment of falls will be done using the current gold standard of collecting monthly reports [45] returned by postal and/or electronic mail, an efficient (1-2 minute completion time) and effective method used by our team and others [41, 46-48]. In two prior studies we obtained 98% of monthly fall reports over 6 months [46, 49]. Participants will be provided with a monthly falls calendar to record falls when they occur, in order to reduce issues of recall and false negatives. Each participant that records a fall will be phoned to confirm that each fall meets the standard definition in order to reduce the risk of false positives, and to obtain information about the fall (e.g., how it occurred) and any resultant injury. An "injurious" fall is one that results in fractures, head injuries, sprains, bruises, scrapes, or serious joint injuries, or where the participant seeks medical care [13]. Of primary interest in the proposed study is the # of falls, with the # of injurious falls and medical care resulting from a fall being used for descriptive purposes of the study population.

Secondary Endpoint: Frailty will be measured using the components of the Frailty Phenotype [29]. The original 5 criteria of the phenotype (shrinking, exhaustion, low activity, slowness, and weakness) were limited to the measures available in the Cardiovascular Health Study [29]. The phenotype can now be measured more accurately with objective measures (e.g., lean body mass rather than self-report weight loss[50]). In this study, we will assess each frailty component using measures that will most accurately capture frailty criteria in the prostate cancer survivor population and where cutoff scores can be appropriately determined. A total frailty score will be calculated in the same manner as that of Fried: $\geq$3 criteria = frail; 1-2 criteria = prefrail; 0 criteria = robust. Since each variable is a continuous measure we will examine changes in each individual frailty component to determine how each intervention may shift frailty among our sample. Criteria are measured as follows:

1. *Shrinking*: Since weight gain is a common side effect of ADT capturing the loss of lean mass that the "shrinking" component of the Frailty Phenotype was intended to capture may be difficult by tracking weight loss alone. Rather, we will measure lean mass by whole body by DXA (Hologic-QDR Discovery Wi; APEX software, v.4.02) scan performed by trained research personnel. The CV for body composition measures in our lab is <1.0%. We will also measure lean mass by bioelectric impedance analysis (BIA; Imp SFB7, ImpediMed, Inc., Australia). DXA is the gold standard approach for measuring body composition, but is expensive and not always available outside of a clinical setting. BIA has been recommended as a technique to measure sarcopenia in the elderly [51] and is as accurate and reliable [52, 53] yet more practical than other types of body composition techniques such as DXA or skinfolds because it is portable and does not rely on extensive technician training and experience [54]. If we can show equal classification and sensitivity to change with BIA we can use this measurement technique instead of DXA in future implementation trials. Cutoffs for sarcopenia have been established. We will use a cutoff score for moderate sarcopenia in men of $\leq$10.75 kg/m^2 based measures from men aged 60+ in the NHANES II database [55]. Since obese, rather than traditionally defined frailty is an emerging concept and our data suggest obese frailty increases risk for falls even more than traditional frailty, we will calculate obesity frailty by substituting BMI>30kg/m^2 for SMI and repeating analyses. We will also record weight on a scale at each visit.

2. *Exhaustion*: We will use the self-reported score on SF-36 Vitality Scale which we have used to characterize exhaustion for frailty in cancer survivors [56] and which has established reliability [57], has been validated in cancer survivors as a fatigue measure[58] and has shown sensitivity to change in response to exercise in adult, older adult and clinical populations, including cancer [59-61]. We will use cutpoints of scores of less than 50.00 (normed) for prostate cancer survivors aged 50-64 years or scores less than 40.00 (normed) for prostate cancer survivors aged 65+ years. Cutpoints are lowest quartile of scale in general U.S. population [57]. The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale will also be administered. It is a 13-item questionnaire. Though not used in frailty assessment, but used to evaluate reductions in cancer-related fatigue from exercise [62], we can also consider changes in the fatigue subscale of the QLQC30 which could be more sensitive in prostate cancer survivors (see below).
3. *Low Activity*: Low activity will be measured by physical activity-related energy expenditure (METS), calculated from self-report physical activity. We will use Fried's original cutpoints for "low activity": <383 kcals per week spent in moderate-vigorous intensity activity measured by the 41-item Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire. [63] CHAMPS is a common and highly reliable [64] measure of physical activity in older adults, including our studies in cancer survivors [33, 49, 65, 66]. We considered using accelerometry to track activity levels but this technique introduces considerable expense and personnel resources. Given our available resources we will be able to conduct a sub-study on 2 study waves (~100 men) to compare objective to self-report methods for tracking activity change over time.
4. *Slowness*: Walking speed will be measured as the fastest time of two 15' walks at a usual pace. Walks will be performed on an electronic gait mat to ensure accurate timing. We will use Fried's original cutpoints for "slowness" in older men of time $\geq$7 seconds for height $\geq$173 cm or time $\geq$6 seconds for height <173 cm. Test-retest correlations for average walk speed are strong: 0.72-0.93[67]. 3 meter Timed Up and Go will also be collected as a measure of slowness.
5. *Weakness*: In contrast to grip strength used by Fried in her original phenotype, lower body strength is more closely linked to falls, mobility, and dysfunction and can be easily obtained using well established timed chair stand test (seconds required to rise from chair 5 times)[68, 69]. Chair stand time $\geq$12 seconds has been shown to predict a 2.4 increased risk of falls in older adults and we will apply this cutoff for "weakness"[70].

We will also assess frailty at baseline using the FRAIL scale self-report measure, as we have done in our previous study [8].

Secondary Endpoint: Physical Function: Physical function will be measured objectively (mobility, balance) and subjectively (perceived function by self-report).

Functional Mobility: The Timed Up and Go (TUG) test is a reliable [71] and widely accepted clinical measure of mobility that evaluates the time that it takes a person to rise from a chair, walk 7 m, turn around a cone and return and sit in the chair [72]. Slower TUG times are associated with an increased risk of falls [73] and disability [69]. Dr. Horak, a Co-Investigator, developed an instrumented version of the TUG test that incorporates wearable sensors to detect changes in mobility that are not apparent from the stopwatch TUG score.[74] The iTUG system can electronically capture individual elements of the TUG test at a very sensitive level to detect small changes over time and decrements in higher functioning patients that might be missed by a stopwatch time. TUG time is our main outcome, but we will examine additional information provided by the iTUG (e.g., segment time, step #) to understand which components of mobility ADT affects. A 7-meter dual task will also be condcuted. A participant will be asked to count

backwards by 3's starting at 99. In addition, standing balance tests will be done as part of the Physical Performace Battery.

Functional Balance: Postural sway is a reliable [75] measure of how well a person can maintain their equilibrium during quiet standing. Increased sway indicates poor balance control and is associated with falls [72]. We will conduct two standard 30-second postural sway test to measure the sway area (m^2/s^3) and amount (m/s^2) and velocity (m/s) of sway during quiet standing with feet together and eyes closed and feet together eyes open using lightweight, inertial wireless sensors worn on the trunk [75]. Lateral sway velocity is the outcome of interest because it is a strong predictor of falls in older adults[76] and may detect changes in balance associated with cancer treatment [77].

Passive monitoring of functional mobility and balance: Because people can perform better in a testing environment than how they normally move in daily life [78], we will also collect gait and balance measures using SmartSox passive monitoring sensors. SmartSox are a new product developed by APDM, Inc, that also manufactures the iTUG and postural sway sensors used in this study. SmartSox are a thin neoprene wrap that is worn under socks throughout the day and provides continuous passive monitoring of gait and balance. In addition to the postural sway measurements listed above, we will ask participants to wear SmartSox sensors for 8-10 hours daily for up to 7 days per measurement period. Data are transmitted the same way as data from the iTUG and postural sway sensors and participants charge the socks each night just like a smart phone. SmartSox passively collect gait and balance measures such as quality and quantity of walking activity. These metrics may be more sensitive indicators of mobility problems since they can detect decrements in gait and balance that are not picked up by traditional timed tests in the clinic or gait laboratory. Participants will document SmartSox use in a daily diary (i.e., date, time put on and taken off each day).

Perceived Physical Function will be measured by self-report using the physical function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; version 3, App. I), a cancer-specific measure and common in studies of prostate cancer survivors, including ours [37, 79].

Flexibility may improve in the control group, so we will measure flexibility in all groups using the standardized Chair Sit and Reach Test for lower body flexibility. This test is designed for and validated in older adults. Lower scores indicate more flexibility.

Study visits may be delivered in-person with additional precautions and/or delivered remotely via video conferencing. In order to determine the validity of remote delivery, participants may be asked to complete both sets of testing at every time point (in-person plus remote). In such cases remuneration will be offered to offset the additional time asked of participants. If delivered remotely, select testing measures will be adapted to this type of delivery. These testing measures include:

1. Height
2. Weight
3. Flexibility (chair sit and reach, see Secondary Endpoint: Physical Function, above)
4. Physical Performance Battery (PPB) (see Secondary Endpoint: Physical Function, above)
5. Passive monitoring of functional mobility and balance (see Secondary Endpoint: Physical Function, above)
6. 3m TUG (see Secondary Endpoint 4. Slowness, above)
7. All surveys (see Primary Endpoints and Secondary Endpoints, above) will continue to be sent out electronically as previously described. If a participant needs a paper survey to complete the survey, one will be provided or their data will be marked as "missed" if study

staff are unable to mail a paper survey to the participant during their outlined testing window.

The following measures will not be collected remotely:

1. DXA scan and BIA (see Secondary Endpoint 1. Shrinking, above)
2. Functional Mobility and Functional Balance (see Secondary Endpoint, above)

Descriptive and Process Measures

Demographic variables and cancer history and treatments will be measured at baseline by an in-house questionnaire. Measures that account for disease extent (presence or absence of metastatic disease), type of ADT (intermittent vs. continuous; use of next generation high potency agents) will be collected. Updated information will be collected at subsequent visits. Measures of weight and height will also be made.

Presence of chronic medical conditions that affect physical functioning will be measured by the Charlson Comorbidity Index and the Functional Comorbidity Index (FCI) [80]. We use both instruments because Charlson provides an index of "sickness" that is commonly reported in studies of older adults, while the FCI provides a different index of the number of conditions that affect a persons physical functioning. We will add two additional conditions to the list of 18 in the FCI to capture vestibular problems and/or peripheral neuropathy that might affect exercise ability and predispose men to fall risk in excess of ADT so that we can control for this in analyses.

Exercise outside the exercise intervention could affect the fall and function outcomes in our study. In addition to using CHAMPS to measure physical activity for the frailty criterion and exercise participation during follow-up, we will also look at individual items to see whether participants significantly increase participation in other types of exercise in addition to their assigned study program.

Adherence. Adherence (% of prescribed sessions completed) will be tracked from attendance logs recorded by the exercise instructor. Adherence data will be used to describe the dose of exercise received by participants. It is expected that men will occasionally miss classes due to travel, illness, or other reasons, thus we must get an accurate estimate of received (exercise) dose in order to generalize our findings.

Acceptability of intervention and self-management of ADT side effects is useful information to guide future dissemination and implementation efforts. We will survey prostate cancer survivor's knowledge of and intent to manage ADT side effects [81] at baseline and assess satisfaction with each exercise program post-intervention [82].

Additional Measures of Interest

Fear of falling may impact a participant's confidence that he can safely engage in a study exercise program. This factor may also change across the intervention. Though this is not a major outcome in the proposed study, we feel it may provide important information about the population and intervention. To assess fear of falling we will use the Survey of Activities and Fear of Falling in the Elderly (SAFFE), [83] that has 11 items representing activities of daily living associated with fear of falling, mobility, and social activities. The SAFFE score is the average of item responses, with higher scores indicating greater fear of falling.

Perceived disability. Though not a specified endpoint for this trial disability and dependence upon others for daily tasks may result from frailty and dysfunction. If either experimental intervention reduces frailty and improves function it may also lower the risk for disability, so that prostate cancer survivors on ADT can remain more independent. We will measure perceived disability using the 16-item disability component of the Late-Life Function and Disability Instrument [84, 85]. Scores range from 0-100, with higher scores indicating less disability.

Cancer treatment related symptoms. Several symptoms that are associated with ADT may impact both exercise tolerance and/or fall risk, but are also possibly ameliorated by exercise. Thus, we will track changes in symptoms across the study to examine whether or not these symptoms moderate or mediate the effects of the different interventions on falls and frailty. All measures will used standardized and widely accepted questionnaires that are cancer-specific when available. The symptoms and their measures include fatigue by the Functional Assessment of Cancer Therapy (FACT) fatigue instrument, pain by the Brief Pain Inventory, vertigo by the Vertigo Symptom Scale, cognition by the FACT-Cog instrument, Anxiety by the PROMIS short form anxiety instrument and Depressive symptoms by the Centers for Epidemiologic Studies Depression scale (CES-D).

Cancer-related loneliness: Participation in group-based exercise may facilitate development of friendships and comradery with others around a shared experience of cancer, which may result in reduced feelings of loneliness. To assess changes in cancer-related loneliness, we will administer a validated cancer-related loneliness questionnaire, the Cancer Loneliness Scale [Adams, 2017], to survivors. We will administer the CLS to newly enrolled participants.

Ancillary study:

Design

This cross-sectional study will consist of collecting up to 7 days of daily mobility via Smartsox and relating mobility characteristics to ADT history, falls in the previous 12 months, objectively measured and self-report frailty, and objectively measured and self-report physical functioning in PC survivors exposed to ADT.

Participant incentive

There will be a $25 remuneration to offset transportation costs for the testing visit.

Measures and Data Collection

Performance testing, frailty measures, and surveys will be administered once. Daily mobility will be collected for up to 7 days. Total time for performance testing and survey completion is ~2 hours. Men complete written surveys on a desktop or laptop computer, unless they prefer to complete paper surveys (~5% of participants in our last intervention trial prefer paper over online). Staff reviews surveys for completeness and follows up with participants in person or by phone on missing data.

Outcome Measures

Daily mobility: Subjects will wear SmartSox (APDM) with inertial sensors embedded into thin, neoprene ankle wraps. The sensors will be worn 8-10 hours a day for up to 7 consecutive days. At the end of the sampling period, participants will return socks to the study team in a pre-paid mailer. Raw data will be stored on the sensors and uploaded to a secure server for analysis after mailed back so wireless access is not necessary. Measures of mobility calculated during daily monitoring include turning quality, activity, and gait quality, and are calculated with proprietary algorithms from APDM. The measures are calculated by combining the 3 axes of linear acceleration with 3 axes of angular velocity and the magnetometer to obtain orientation of the limb in space. Wireless synchronization, unique to the APDM Opal sensors, allows precise temporal binding of data across limbs. Walking bouts and turning events are first identified, followed by calculation of metrics within each walking bout and turning event. Participants will document SmartSox use in a daily diary (i.e., date, time put on and taken off each day).

Fall history: Falls in the last year and injuries from falls will be collected using a falls survey.

Frailty: The five components of the frailty phenotype (shrinking, exhaustion, low activity, slowness, and weakness) will be collected using the following measures (described in detail above):

Shrinking – Lean mass as assessed by DXA and BIA

Exhaustion – Self-reported score on the SF-36 Vitality Scale, FACIT Fatigue scale

Low activity – measured by physical activity-related energy expenditure (METS), calculated from self-report physical activity. We will use Fried's original cutpoints for "low activity": <383 kcals per week spent in moderate-vigorous intensity activity measured by the 41-item Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire.

Slowness – Walking speed, measured as the fastest time of two 15' walks at a usual pace. 3 meter Timed Up and Go will also be collected as a measure of slowness.

Weakness – Timed chair stand test (seconds required to rise from chair 5 times)[68, 69].

We will also assess frailty using the FRAIL scale self-report measure, as we have done in our previous study [8].

Demographic variables and cancer history and treatments will be measured by an in-house questionnaire. Measures that account for disease extent (presence or absence of metastatic disease), type of ADT (intermittent vs. continuous; use of next generation high potency agents) will be collected.

Objective physical functioning will be assessed using measures of functional mobility and functional balance, as described above.

Perceived physical functioning will be measured by self-report using the physical function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; version 3, App. I),

Perceived disability will be measured using the 16-item disability component of the Late-Life Function and Disability Instrument, as described above.

Presence of chronic medical conditions that affect physical functioning will be measured by the Charlson Comorbidity Index, as described above.

Other measures: User experiences while wearing SmartSox will be collected with a SmartSox User Questionnaire.

Ancillary study #2:

Design

We will use two complementary secondary analyses to characterize relationships between physical and cognitive aging in men with prostate cancer treated with ADT, based in a model of cancer treatment- induced accelerated aging[39]. **Aim 1** will use baseline data from the GET FIT Prostate clinical trial[73] (N=284) to investigate associations between cognitive aging (cognitive functioning, depression, fatigue) and physical aging (objective and perceived mobility). **Aim 2** will use baseline data from a subset of participants in GET FIT Prostate who completed additional assessments of physical aging at home using wearable sensors (daily life mobility; N=65). From

Aims 1 and 2, we will have a unique opportunity to characterize cross-sectional relationships among latent domains of physical and cognitive aging and to identify which measures are the most interrelated and strongest contributors to the observed associations.

Conceptual Framework

According to Carroll et al.'s model of cancer treatment-related accelerated aging[39], physical and cognitive aging are driven by cancer treatment-induced cellular stress/damage and systemic inflammation. In this model, physical aging manifests as mobility impairment and increased risk of frailty and comorbidities, while cognitive aging is comprised of both behavioral and cognitive features, including depression, fatigue, and cognitive deficits. This model is based largely on studies of chemotherapy and radiotherapy, but we believe it can also be a model to study the impact of ADT on accelerated aging. Here, we will use this conceptual framework to guide our approach to understanding how ADT leads to interrelated physical and cognitive aging.

Measures

Physical aging measures (Aim 1):

Objective physical functioning will be assessed using measures of slowness, weakness, functional mobility, and functional balance, as described above.

Perceived physical functioning will be measured by self-report using the physical function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; version 3, App. I) and the overall functioning subscale of the Late-Life Function and Disability Instrument (LLFDI).

Physical aging measures (Aim 2):

Daily mobility will be assessed using measures derived from SmartSox, including activity, turning, and gait quality/quantity, as described above.

Cognitive aging measures (Aim 1 and 2):

Cognitive functioning will be assessed using cognitive function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; version 3, App. I) and the FACT-Cog Instrument.

Depression will be assessed using the Centers for Epidemiologic Studies Depression scale (CES-D).

Fatigue will be assessed using the self-reported score on SF-36 Vitality Scale and the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale.

Other variables of interest (Aims 1 and 2):

Demographic variables and cancer history and treatments will be measured by an in-house questionnaire. Measures that account for disease extent (presence or absence of metastatic disease), type of ADT (intermittent vs. continuous; use of next generation high potency agents) will be collected.

4.0 STUDY POPULATION

For this study, we will recruit prostate cancer survivors treated with ADT and at risk for frailty (N=360).

Ancillary study: we will recruit prostate cancer survivors treated with ADT (N=130).

Ancillary study #2: For Aim 1, we will use cross-sectional baseline data from participants who enrolled in the parent study (GET FIT Prostate) (N=284). For Aim 2, we will use cross-sectional baseline data from GET FIT Prostate for the subset of participants from Aim 1 who completed assessments of daily life mobility (n=65).

5.0 INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

- Diagnosed with histologically confirmed prostate cancer (confirmed by self-report on Health History Questionnaire. In the case a participant isn't able to confirm this criterion, a letter will be sent to his physician.)
- Currently on ADT for ≥ 6 months OR not currently receiving ADT, but received ≥ 6-month course within the last 10 years (confirmed by self-report on Health History Questionnaire. In the case a participant isn't able to confirm this criterion, a letter will be sent to his physician.)
- If they have had other treatment, such as surgery, radiation or chemotherapy, it must have been completed ≥ 6 weeks prior to enrollment and no concurrent adjuvant therapy other than ADT for prostate cancer (confirmed by self-report on Health History Questionnaire. In the case a participant isn't able to confirm this criterion, a letter will be sent to his physician)
- Meets criteria for having experienced ≥1 fall in the last year (confirmed by self-report on Health History Questionnaire) or if no falls, meets criteria for slow TUG time (≥12.0 seconds) or slow chair stand time (≥10.0 seconds) (confirmed by baseline screening testing)

Exclusion Criteria:

- Current participation in moderate or vigorous lower-body strength training two or more times per week for 30 minutes or more or participating in tai chi two or more times per week for 30 minutes or more (confirmed by self-report on Health History Questionnaire or by discretion of the Principal Investigator)
- Cognitive difficulties that preclude answering the survey questions, participating in the exercise classes or performance tests, or providing informed consent (Confirmed by the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone.)
- A medical condition, movement or neurological disorder, or medication use that contraindicates participation in moderate intensity exercise (Confirmed by self-report on the Health History Questionnaire, and/or by physician clearance. If in the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone, contraindications other than those identified by the patient or physician are present, she may consider the participant ineligible.)
- Not medically cleared for participation in moderate intensity exercise. (Confirmed by physician clearance.)
- Knowingly unable to attend >75% of the intervention classes due to conflict with the designated time of day, days of the week, and/or location for the exercise class which

they initially enrolled. (Confirmed by documentation in the Case Report Form titled “CRF - Participant Contact Info_GET FIT Prostate”)

- Not fluent in English and therefore incapable of answering survey questions, participating in class, following directions during performance testing, and providing informed consent when English is the language used. (Confirmed by documentation in the Case Report Form titled “CRF - Participant Contact Info_GET FIT Prostate” or the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone.)

Ancillary study: Participants in the ancillary study will not be participating in exercise, so exclusion criteria related to the exercise intervention have been removed. We have also removed the fall risk inclusion criterion in order to include men with higher levels of physical functioning.

Inclusion Criteria:

- Diagnosed with histologically confirmed prostate cancer (confirmed by self-report on Health History Questionnaire. In the case a participant isn’t able to confirm this criterion, a letter will be sent to his physician.)
- Currently on ADT for ≥ 6 months OR not currently receiving ADT, but received ≥ 6-month course within the last 10 years (confirmed by self-report on Health History Questionnaire. In the case a participant isn’t able to confirm this criterion, a letter will be sent to his physician.)
- If they have had other treatment, such as surgery, radiation or chemotherapy, it must have been completed ≥ 6 weeks prior to enrollment and no concurrent adjuvant therapy other than ADT for prostate cancer (confirmed by self-report on Health History Questionnaire. In the case a participant isn’t able to confirm this criterion, a letter will be sent to his physician)

Exclusion Criteria:

- Cognitive difficulties that preclude answering the survey questions, participating in performance tests, or providing informed consent (Confirmed by the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone.)
- A medical condition, movement or neurological disorder, or medication use that contraindicates participation in performance testing (Confirmed by self-report on the Health History Questionnaire and/or Charlson Comorbidity Index questionnaire. If in the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone, contraindications other than those identified by the patient are present, she may consider the participant ineligible.)
- Not fluent in English and therefore incapable of answering survey questions, following directions during performance testing, and providing informed consent when English is the language used. (Confirmed by documentation in the Case Report Form titled “CRF - Participant Contact Info_GET FIT Prostate” or the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone.)

Ancillary study #2: The sample for Aim 1 will have the same eligibility as the parent study. The sample for Aim 2 will have the same eligibility as the 1st ancillary study.

6.0 VULNERABLE POPULATIONS

This study will not include any vulnerable populations. We will not collect any information about subjects' status as prisoners or pregnant women. Children will not be included because they do not get prostate cancer.

7.0 SETTING

The primary testing site will be at the Oregon Health & Science University (OHSU) Knight Cancer Research Building while exercise training will be offered at OHSU and several community sites serving different geographic regions of the Williamette Valley. Study visits and exercise training may also be delivered remotely via video conferecing. Conferences are set up by a private link sent to participants by email. Any data recorded during training or study visits will be entered directly into databases on staff computers**.**

8.0 STUDY PROCEDURES AND SCHEDULE OF EVENTS

Screening tests and procedures:

Some potential participants will be sent a MyChart recruitment invitation via an email notification, as below, with the Subject "New Research Study" instructing them to log into MyChart to learn more and respond. The text of this invitation and a description of the MyChart recruitment process is contained in *Recruitment - EPIC MyChart procedures_20200521*. The link in the MyChart invitation will take the potential participant to their MyChart homepage with a link to a description of the study. The text for the study summary is contained in *Recruitment - EPIC MyChart patient facing text* and *Recruitment-EPIC MyChart patient facing text-remote*. Potential participants will express interest or decline by pressing the associated buttons in MyChart, or they will not respond. If the potential participant indicates interest, they are automatically associated to the study in Epic with a status of "interested;" the study remains listed on the patient's Research Studies page in MyChart, and the study team immediately receives an in basket notification in Epic so that they can follow up with the patient. If the patient clicks "No, Thank You" this study will no longer appear on their Research Studies page in MyChart, and the patient is automatically associated to the study in Epic with a status of "declined." The recruitment script for contacting potential participants that express interest in the study is contained in the document *Screening – GET FIT Prostate Phone Screen_revised 20190904 and Screening – GET FIT Prostate Phone Screen_Remote*.

Interested participants will be screened either by phone or in person using an IRB approved screening script. After initial screening, potentially eligible men will be scheduled for consent and baseline screening and possible further baseline testing in qualified men. Screening includes review of fall history in the past year, a 3-meter Timed Up and Go walk at usual pace, and standing up and down from a chair five times as fast as safely possible. The testing session will include DXA, performance testing and survey completion and will be repeated at 3- and 6-mos. (post-intervention), and 6 mos. after completion of the intervention (follow-up). Total time for performance testing and survey completion is ~2-2.5 hours. Men will complete written surveys on a computer at baseline and online for follow-up visits, unless they prefer to complete paper surveys. Staff will review surveys for completeness and follow up with participants in person or by phone on missing data. To reduce bias we will retain blinding of the research assistants who conduct the testing visits, by having the Project Director provide each participant with an envelope that contains his random group assignment *after* baseline testing is complete. Qualified men will

be randomly assigned to 1 of 3 groups: 1) tai ji quan, 2) strength training or 3) stretching control. To avoid confounding and differential tolerance to exercise by ADT history and age, block randomization stratifying for timing of ADT (past or current) and will be done using EXCEL to generate random assignments from each block. Assignment will be in random blocks of 6 to 9 within each wave (~42-48 men) to facilitate even enrollment and to prevent the Project Director from predicting group assignment.

Intervention, tests or procedures:

Regardless of group assignment, all participants will be expected to engage in 1-hr exercise sessions, 3 d/wk for 6 months. Each intervention minimizes reliance on expensive equipment and emphasizes simple exercises based on functional movements. It is difficult to precisely equilibrate the total volume (intensity and duration) of exercise performed between experimental groups because the nature of each modality is so different. Both will be matched as closely as possible in progression from the low to high end of the range for moderate intensity over the first 3 months of the intervention. They will remain at a constant overload for the last half of the intervention. For safety reporting purposes, a monthly Adverse Event Survey will be sent electronically or completed over the phone. More details about this survey can be found under section 19.1 Monitoring Plan.

Follow up tests and procedures:

After the completion of the 6 month exercise intervention, all men will be followed for an additional 6 months after formal training stops. Men will continue to track their falls during the follow-up period using the same monthly reports employed in the intervention phase. We recognize that men may wish to maintain their exercise habits after formal training stops and we will not discourage them from doing so. During the follow-up period, exercise questionnaires will be used to track participation in home or community exercise programs and will be collected at the 9- and 12-month time periods.

The total duration of an individual subject's participation in the study is 12 months. Certain data (questionnaires, adverse events follow-up, and Release of Information forms) may be collected after this 12-month period, when a participant is off study, using IRB-approved language.

When participants drop out of the research their data will be retained for analysis. If a participant becomes ineligible during the study he will be withdrawn by the investigator and data will no longer be collected; however, in these cases the participant would be allowed to continue in the study exercise program as long as the reason for ineligibility does not contraindicate exercise participation.

The investigator may choose to withdraw a participant without their consent if his health changes and the study is no longer in their best interest, if new information becomes available, if he does not follow the study rules, and/or if the study is stopped by the IRB.

SCHEDULE OF EVENTS

Procedures	Eligibility Screening	Baseline Testing	Intervention (Month 1-6	Post-Intervention (Month 7-12)	3-Month Testing	6-Month Testing	9-Month Testing	12-Month Testing
Pre-screening eligibility	X							
Consent form	X							
Demographics – demographic questionnaire		X						

Procedures	Eligibility Screening	Baseline Testing	Intervention (Month 1-6	Post-Intervention (Month 7-12)	3-Month Testing	6-Month Testing	9-Month Testing	12-Month Testing
Health history questionnaire		X			X	X		X
Comorbidities – FCI		X			X	X		X
Charlson Comorbidity Index		X						X
Disability - LLFDI		X			X	X		X
Fear of falling - SAFFE		X			X	X		X
Brief Pain Inventory		X			X	X		X
PROMIS Anxiety Short Form		X			X	X		X
Depression: CES-D		X			X	X		X
Vertigo		X			X	X		X
FACT-Cog		X			X	X		X
Cancer Loneliness Scale		X			X	X		X
Falls + AEs-Monthly			X	X				
Falls-Quarterly					X	X	X	X
Falls-Past year	X	X						
Exercise follow-up							X	X
FRAILTY								
Shrinking-BIA, DXA		X			X	X		X
Exhaustion-SF-36 Vitality Scale		X			X	X		X
FACIT-Fatigue		X			X	X		X
Low Activity-CHAMPS		X			X	X		X
Slowness-15' usual pace walk		X			X	X		X
Slowness- 3 meter TUG	X	X			X	X		X
Weakness-Chair stand test	X	X			X	X		X
FRAIL scale		X						
PHYSICAL FUNCTION								
Flexibility		X			X	X		X
Functional Mobility-7 meter TUG and dual task 7-meter TUG		X			X	X		X
Functional Balance-Postural sway, PPB standing balance		X			X	X		X
Physical functioning-6-minute walk		X			X	X		X
Passive monitoring of functional mobility and balance (SmartSox)		X				X		
Perceived Physical Function-EORTC QLQ-C30		X			X	X		X

Ancillary study:

Screening tests and procedures:

Some potential participants will be sent a MyChart recruitment invitation, following the procedures described above. The text for the study summary is contained in *Recruitment - EPIC MyChart patient facing text_SmartSox.*

Interested participants will be screened by phone using an IRB approved screening script. The recruitment script for contacting potential participants that express interest in the study is contained in the document *Screening - GET FIT Prostate Phone Screen_SmartSox.* After initial screening, eligible men will be scheduled for a consent and testing visit.

Study tests and procedures:

The testing session will include performance testing, survey completion, and instruction on the use of SmartSox. Total time for performance testing and survey completion is ~2 hours. Men will complete written surveys online, unless they prefer to complete paper surveys. Staff will review surveys for completeness and follow up with participants in person or by phone on missing data.

Participants will wear SmartSox for up to 7 days following the testing visit. After dressing in the morning, participants will wear SmartSox (APDM) with inertial sensors embedded into thin, neoprene ankle wraps. The sensors will be worn up to 8 hours a day for up to 7 consecutive days. Socks are inserted into a docking station to charge each night. At the end of the sampling period, participants will return socks to the study team in a pre-paid mailer. Participants will document SmartSox use in a daily diary (i.e., date, time put on and taken off each day). Participants will complete a SmartSox User Questionnaire at the end of the sampling period.

The total duration of an individual subject's participation in the study is 1 week.

SCHEDULE OF EVENTS

Procedures	Eligibility Screening	Testing Visit
Pre-screening eligibility	X	
Consent form	X	
Demographics – demographic questionnaire		X
Health history questionnaire		X
Charlson Comorbidity Index		X
Disability - LLFDI		X
Falls-Past year		X
FRAILTY		
Shrinking-BIA, DXA		X
Exhaustion-SF-36 Vitality Scale		X
FACIT-Fatigue		X
Low Activity-CHAMPS		X
Slowness-15' usual pace walk		X
Slowness- 3 meter TUG		X

Procedures	Eligibility Screening	Testing Visit
Weakness-Chair stand test		X
FRAIL Scale		X
PHYSICAL FUNCTION		
Functional Mobility-7 meter TUG and dual task 7-meter TUG		X
Functional Balance-Postural sway, PPB standing balance		X
Physical functioning-6-minute walk		X
Passive monitoring of functional mobility and balance (SmartSox)		X
Perceived Physical Function-EORTC QLQ-C30		X
SmartSox User Questionnaire		X

Ancillary study #2: There are no study procedures because this is a secondary analysis of data collected through the parent study and ancillary study #1.

9.0 DATA AND SPECIMENS *(REQUIRED)*

a) Handling of Data and Specimens

All contact information collected from the study, including name, mailing address, phone number and email address, will be stored on an encrypted and password protected computer drive in the OHSU Knight Cancer Research Building that only IRB approved persons have access to.

All other data collected for this study including answers from the health history form (e.g. DOB, education, income, demographics, as well as cancer specific information such as diagnosis, type & dates of cancer treatments), answers to the study surveys, and results from the physical tests will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.

Data that may be collected from a patient's electronic medical record would include contact information including phone number, mailing address and email address, as well as cancer specific information such as diagnosis, type & dates of cancer treatments. Any data collected will be stored on an encrypted and password protected computer drive in the OHSU Knight Cancer Research Building that only IRB approved persons have access to.

Consent forms and any surveys that were filled out on paper will be stored in a locked cabinet in a locked, secure room in the OHSU Knight Cancer Research Building.

Data from the HHQ, surveys and physical tests will be transported by secure electronic transmission (i.e. secure, encrypted email or stored on a secure shared drive such as Box).

The PI will be responsible for the receipt or transmission of the data.

Data will be stored until data analysis is complete and then the data will be transferred to a repository.

b) Sharing of Results with Subjects

Results of the physical tests will be shared with the subjects.

c) Data and Specimen Banking

Data from this study will be banked in a repository for future use as part of this protocol. Data may be stored indefinitely. Access to data is restricted to study personnel. Data released to other investigators will be labeled with only the code assigned to each participant at enrollment.

After the study is complete, all contact information (e.g., name, mailing address, phone number) and data from the HHQ, study surveys and physical tests will be stored in a private locked-repository (IRB# 7553) at OHSU Knight Cancer Research Building. The contact information will be stored separately from the other data. The repository will be managed by Dr. Kerri Winters-Stone, the Principal Investigator of the study. All of the data from the surveys and physical tests will be coded with a unique ID number that doesn't contain any PHI. The list matching the PHI and the ID number is stored in a password protected document on a password protected computer drive in the OHSU Knight Cancer Research Building that only IRB approved persons have access to. Only IRB approved research staff will have access to the password and computer drive where this record is stored. Any requests made for the use of the data will be evaluated by the repository guardian, Kerri Winters-Stone, who will create a subset of eligible data using OHSU IRB confidentiality procedures. The repository guardian will apply an algorithm to the ID numbers on the data subset, therefore, creating a new unique identifier for each data that will be used. This will ensure that only the guardian can link the data back to original study ID numbers and corresponding PHI. Only the guardian will have access to this algorithm. Any future human subject research study that wants to use the data or contact information from the repository will require separate IRB approval. The usage requirements will be limited to the principal investigator, co-investigators and associates from the original research studies. Any future study requesting use of the data must either be related to the original research study or explore new and innovative research questions approved by the guardian.

10.0 RISKS TO SUBJECTS

The risks to human subjects include potential adverse effects of exercise. Risks of participation include tiredness from answering research questions or participating in exercise, anxiety about ability to read surveys or reach exercise goals, discouragement about ability to exercise, worry about loss of confidentiality/privacy, and perception of coercion to participate. Additional risks to participation include radiation exposure. There is minimal radiation exposure associated with a whole body DXA scan (<1 μSv), which is less than half of radiation received on a one-way trip from California to New York and has negligible health risks.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

The Oregon State Cancer Registry (OSCaR) will be used to recruit participants. Established in 1996, the registry is nationally recognized for the accuracy and completeness of its data. All tumors, except common skin cancers, are required to be reported by hospital registries, clinics, cancer treatment centers, and physician offices in Oregon and neighboring states where Oregon

residents are treated. Patient's data is reported, checked for quality assurance, and entered into OSCaR within six months of diagnosis. OSCaR procedures are well established and designed to protect persons in the registry. When each person's data is entered in the registry, the individual is sent a letter asking if he is willing to be contacted about opportunities to participate in research studies. Very few refuse to be contacted.

Patients will be identified by OSCaR for their cancer type, cancer treatment (surgery, radiation and/or chemotherapy), and zip code. OSCaR will then send identified patient data including the patient's physician information to our team using secure electronic transmission (i.e. encrypted flashdrive, secure encrypted email or stored on a secure shared drive such as Box). Data from OSCaR is only being used for purposes of identifying eligible patients and from this point forward is no longer involved in the research. Our team will then send an information letter about the study to listed physicians for identified persons in the registry, notifying the physician that their patient will be sent information about the study. Physicians who determine that their patients should not receive study information are asked to return a form to the study investigator within a 3-week period. These persons will no longer be considered eligible to receive study information. All other potential participants will be sent an information letter briefly describing the study along with a response form and contact information of the research team. Persons who are interested in receiving more information about the study are asked to either contact our team directly (phone, email, text) or complete the response form and return it to our team. For all response forms returned to our team and in response to all other forms of inquiry, a member of the research staff will then contact interested persons to provide more study information to them and to screen for eligibility if they indicate a willingness to participate. Participants will also be recruited via a study information mailing through the OHSU Cancer Registry and from various hospital systems such as Tuality Healthcare, Adventist Health, Providence, Legacy, Kaiser, and community oncology clinics such as Compass Oncology and interested participants will contact us if they would like to learn more about the study and to check for eligibility. Additional OHSU patients may be recruited by gathering patient demographic information from OCTRI's Cohort Discovery, OCTRI's Research Data Warehouse, and OHSU's Medical Records. Recruitments will occur via letters, e-mails, phone calls, or informational announcements through MyChart. In addition we will recruit at community events, such as patient conferences and fundraisers and through study advertisements placed through various media outlets (i.e., internet, newspaper, radio).

Dr. Hung, all urologic oncologists with specialties in medical, surgical and radiation oncology, respectively, on the research team and co-investigators, will consult on eligibility issues as needed during recruitment. Eligible persons will come to the OHSU Knight Cancer Research Building to be consented and undergo baseline measures.

Ancillary study: In addition to the recruitment methods listed above, we will reach out to current and past study participants who have given their permission to be contacted about future study opportunities.

b. Protection Against Risk

Participant safety and side effects during exercise. As with any form of exercise, there is a slight risk of injury. We have not had a single participant drop out of a study due to an injury related to the exercise program; however, as with any study in older adults, exercise adherence has been affected by minor musculoskeletal complaints and are typically exacerbations of pre-existing orthopedic conditions. We will take the following steps to reduce the risk of injury and symptoms/side from exercise training: 1) Physician clearance: We will send a notice to each participant's oncologist (or primary care provider) asking him or her to clear the participant for participation in physical performance testing and any of the study exercise programs prior to beginning exercise training. If a man's physician does not clear him for participation we will inform the participant and refer him to her physician for clarification of the decision, 2) Monitor for and treat early musculoskeletal symptoms: From experience in our prior trials we have developed an

injury prevention education and monitoring program. At the beginning of each participant's start in the intervention he is provided general injury prevention information from the Project Director and exercise trainer. During the intervention the exercise trainer will consult with the Project Director on any reported exercise-related injuries and/or physical complaints from participants that affects their ability to do their exercise program. The Project Director will consult with participants on an individual basis, as needed, and will advise on treatment of their injury/complaint and when referral to a health practitioner is appropriate. The Project Director will work with the study team to track minor and major complaints and injuries in order to evaluate the overall safety and appropriateness of the study interventions for the study population.

During testing visits, if a participant experiences tiredness, he will be told he can stop answering research questions, or participating in performance or clinical testing, and begin again at a later time. Surveys are administered electronically via a web-portal, unless a participant requests paper surveys (usually <5% of a sample). With on-line surveys participants can stop and restart surveys at their leisure, which can reduce tiredness and burden for participants. If tiredness occurs during exercise sessions, participants may rest as often as needed. If a participant is anxious about ability to read surveys, we will offer to ask the questions verbally and fill out the survey by telephone, if anxious about ability to reach exercise goals or discouraged about ability to exercise, Project Director, in consultation with the PI will problem-solve and support the participant in changing goals or developing alternative methods to meet goals. If a participant is worried about privacy and confidentiality of data, the Project Manager will discuss the methods for maintaining confidentiality: individual data will be identified only by a study ID number and only one computer file will link ID numbers with identifiable data; all computer records will be protected by a password known only to authorized study personnel; paper documents, such as surveys or computer disks, will be kept in locked files, and results will presented as group data only. To prevent the perception of coercion to participate, participants will be told they may decide to discontinue participation in the study at any time, that non-participation will not affect their usual care at their local clinic or at OHSU, and that data on non-participation will be kept confidential, using the methods described above.

To minimize risk against excess radiation exposure from DXA, whole body DXA scans will be conducted by a trained Research Assistant. Whole body DXA scans will be performed according to standard protocols which allows for early repositioning to minimize patient exposure.

During remote exercise and testing sessions, additional safety precautions will include: 1) Providing safety recommendations specific to exercises and/or assessments (i.e., standing near a wall for balance activities) 2) Adapting the exercise protocol as necessary (ie. limit weight.) 3) Verifying address of remote exercise location (i.e., home address), should the exercise instructor or Research Assistant need to call 911 in an emergency 4) Ensuring that emergency contact information is up-to-date and readily available.

Ancillary study: Participants in the ancillary study incur no risk from exercise.

11.0 POTENTIAL BENEFITS TO SUBJECTS

Participants may or may not personally benefit from being in this study.

12.0 TIMELINE & MILESTONES

	Y1				Y2				Y3				Y4				Y5			
Development	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Finalize protocols, databases	X	X																		
Hire/train research assistants			X															X		
Hire/train exercise instructors			X			X				X				X						
Recruitment & initial testing																				
Recruit, enroll, baseline visit			W1		W2r	W3			W4r	W5		W6	W7	W8r						

Intervention and evaluation																				
Start 6-month intervention				W1		W2r	W3			W4r	W5		W6	W7	W8r					
Mid- & post-intervention visits				X	X	X	X	X	X	X	X		X	X	X	X				
6-month follow up visit						W1		W2r	W3			W4r	W5			W6	W7	W8r		
Data analysis & publication																				
Data cleaning and analysis							X	X	X	X	X	X	X	X	X	X	X	X	X	
Present and publish results																			X	X

Participants are recruited in 8 waves (W1, W2, ...); "r" after wave abbreviation indicates a regional exercise site; Quarters are approximate time points

Ancillary study timeline:

	Y1			
Activity/Milestone	Q1	Q2	Q3	Q4
Develop ancillary project	X			
Enroll participants into ancillary study and collect data		X	X	
Ongoing data analysis (ADT, SmartSox, survey)		X	X	
Analyze data and submit manuscripts			X	X

13.0 BIO-STATISTICAL CONSIDERATIONS

Power and Sample Size

We have powered the sample size based on our primary aim. In older adults, 20%-30% of community-dwelling elders are likely to fall within 1 year [11] and Li and others have reported a reduction in fall risk of 47% from 3 [86] or 6 [41] months of tai ji quan exercise. We are using an effect size for tai ji quan to power for both interventions because we have these data available from our prior work and effects sizes for strength training are similar to tai ji quan [87]. Our study will determine if strength training is as effective as tai ji quan. Using PASS 2008[88], based on a negative binomial regression model [89], at alpha = .05, the variance shared among the dummy vectors representing treatment (R^2=.25), and an estimate of the overdispersion parameter (Phi) of 2.5, a sample size of n=300 (n=100 per group) participants will provide 80% power to detect at least a 47% reduction in the fall incidence rate over six months by being in either of the 2 exercise groups versus control. To protect against an estimated attrition of ~17% during the intervention period, 120 participants will be randomized per group (total sample size: N=360). The attrition estimate is conservatively based on the highest attrition rate from our prior strength training trials in prostate cancer survivors (0% and 16% attrition in 6 and 12 month trials, respectively [37, 39]). Though the total # of falls is the primary endpoint, the sample size of N=300 also provides sufficient power to detect differences between experimental and control groups on secondary outcomes of frailty and physical function. We and others' have data on the effect of exercise on individual components of frailty in prostate cancer survivors on ADT and self-report physical function. With a sample of N=100 per group we have a sufficient sample to detect a difference in 2.5% of lean body mass [90, 91], a 4 sec. faster chair stand time [37, 91], a 1.1 sec. faster gait speed [91], and a 9% difference in self-report physical function scores [37].

All analyses will retain each participant in the group he was randomly assigned regardless of missing data or drop out status (i.e., intention to treat). We will track medical treatment changes and disease progression during the study to describe the sample or justify why participants exited the study. In the unlikely event of a large subgroup, these data could be used for exploratory subgroup analysis to suggest directions for future research. Age, timing of ADT (current vs. past), fall history at enrollment and baseline frailty will be considered as possible covariates in all analyses. Age and timing of ADT (past vs current) are included since they may affect exercise tolerance and/or responsiveness to exercise training; fall history is included because we want to examine the efficacy of the interventions to reduce falls in men with a fall history and prevent falls

among men who have not recently fallen. Analyses will be conducted in Stata, R, and/or Mplus statistical software packages. Full information maximum likelihood estimation (FIMLE) will be used to estimate the models, as appropriate, because it is less biased and more efficient than other techniques for handling missing or incomplete data[92].

Aim 1: Compare the relative efficacy of tai ji quan and strength training to prevent falls*:* We will determine the efficacy of tai ji quan and strength training by comparing each of them to the control condition while adjusting for important covariates using negative binomial regression models which will analyze total number of falls per participant that occur from baseline to 6 months. A negative binomial regression was chosen over a Poisson regression for modeling the count data because of the overdispersion that is common with actual research data. [88, 93] Intervention type will be entered into the model as 2 dummy variables, with the reference group being the control group. This will allow a comparison of the each of the intervention groups against control. *A second* model will be run with strength training as the reference category to compare the intervention groups to each other. In additional to standard ITT analysis, the impact of participants who drop out of the study on the falls outcome will be examined in a secondary data analysis. A significant incidence rate ratio (IRR) less than 1.0 for the dummy vector representing tai ji quan and/or strength training would provide support for the hypothesis that the respective intervention reduced the rate of falls compared to the control group.

Aim 2: To determine and compare the efficacy of tai ji quan training and strength training to reduce frailty and dysfunction*:* Each participant will be classified as frail, pre-frail or robust based on his total frailty score (see **Measures**). We hypothesize that the number of men classified as frail or pre-frail will decrease over the course of the study in the tai ji quan and strength training groups compared to control. Formal tests of frailty hypotheses will be conducted in a generalized mixed effects modeling framework as implemented in the R statistical computing environment. [94] Frailty category will be the multinomial dependent variable (with “robust” as the reference group) and study time point (0, 3 and 6 mos.), group (control as the reference group) and the group x time interactions will serve as predictors. [95] We will also run a second model with strength training as the group reference category to compare the two experimental groups to each other. Significant group x time interactions will indicate that the distribution of frailty between the groups (e.g., tai ji quan vs. control) is different across time. For significant interactions, additional contrasts testing for frailty differences will be examined to describe the pattern of change across time. Group differences across time in the continuous physical function and individual frailty measures will be tested in a linear mixed effects modeling framework [94] to estimate the trajectory of change in each dependent variable across time for each individual in each group, and then comparing the average trajectories across groups. The primary effect of interest is a cross-level interaction. Specific hypotheses about treatment group effects will be specified by adding dummy variables and hypotheses will be tested through group x time interactions (as above). We will also evaluate the practical significance of the interventions by summarizing results with respect to effect size.

Aim 3: Determine how well the benefits of each intervention persist after structured training stops: We will use the same modeling strategies described above for each outcome (i.e., negative binomial regression, multinomial/linear mixed effects models). However, we will perform the analyses piecewise, with a change point occurring at 6 months. Of particular interest is whether the observed effects for the treatment groups differ or remain the same after the change point. In addition, we will examine whether participation in exercise following the end of the intervention moderates the persistent effect of the intervention on study endpoints. We will categorize the type of exercise participants engaged in (i.e., walking/aerobic, strength training, tai ji quan, stretching) for at least 50% of the follow-up period. These categories will then be dummy coded and entered into the analyses outlined above, along with the product of these dummy vectors and treatment to represent the interaction. A significant coefficient for the product term would indicate that continued exercise modifies the effect of the intervention on falls, frailty, or physical function. This

analysis will allow us to determine whether continued participation in an exercise program maintained improvements for an intervention group or a lack of participation caused a loss of improvements in an intervention group, and whether control participants who begin programs similar to the intervention programs improve in outcomes.

Exploratory Aim: Determine patterns and predictors of types of men who benefit the most. We will use a growth mixture modeling (GMM) approach using Mplus to explore there are distinct types of men (based on age, baseline frailty, cancer stage, ADT duration and timing, other treatments, etc.) who benefit most from the intervention(s). GMM is a type of clustering technique that can simultaneously handle longitudinal data and multiple measures to identify distinct subgroups of patients who have different responses to an intervention. For longitudinal outcomes (e.g., Aim 2), we will employ GMM to identify distinct patterns of change in subpopulations with varying response (growth) trajectories and unique variances reflecting homogenous within-trajectory growth. Patients will be assigned to the "most likely class" or pattern of change over time (e.g., men who improve most from an intervention) and follow-up analyses (e.g., multinomial regression) will be conducted to describe the demographic and clinical characteristics of patients who are classified into different subgroups.

Additional Analyses

Injurious falls: Though the proposed study is not powered to examine reductions in injurious falls from the intervention, we will conduct an additional analysis on this important outcome. An injurious fall is one that results in fractures, head injuries, sprains, or serious joint injuries, or in a participant seeking outside medical attention. We will conduct this analysis among the subsample that had at least 1 fall using logistic regression.

Mechanisms of intervention effects on falls: We can use strength and stability measures to identify the mechanism(s) by which each exercise approach may reduce falls, strengthening support for exercise as a fall prevention strategy. We will test 3 mediators, muscle strength (chair stand time) and stability (walk speed and postural sway) as possible mediators because both measures may be affected by each intervention and each possible mediator is a major risk factor for falls. Mediation of the intervention effect by changes in performance measures will be analyzed using Mplus. A manifest model will be tested with the dummy vectors representing tai ji quan and strength training as exogenous variables, change in strength and as endogenous variables (mediators), and number of falls over the intervention period as an endogenous variable (outcome). Significant indirect parameter estimates based on standard errors using the multivariate delta method from the treatment variables to number of falls through changes in strength and stability would provide support for mediation.

Potential moderators of sustained exercise after the intervention: Linear and logistic regression models will be used to explore different predictors (e.g., age, comorbidities, timing of ADT, etc.) of adherence to exercise after structured training stops.

Ancillary study:

Analysis plan: We will use standard parametric and nonparametric statistical tests as appropriate (e.g., t-tests, Wilcoxon rank sum) to test the relation between gait and turning measures at home and ADT history, frailty category, faller status, and disability. We will then fit multivariable models (e.g., linear, logistic) to predict each outcome from Smartsox measures while including important control variable such as age, disease severity and comorbidities. Model assumptions will be thoroughly investigated and alternative estimation procedures will be applied should any violations occur.

Ancillary study #2:

Aim 1: We will use canonical correlation analysis (CCA) to evaluate relationships between physical and cognitive aging measured at a single timepoint. CCA is a method for evaluating

relationships between two sets of variables; the method is used to generate canonical variates, which represent latent constructs within each group of variables (similar to principal components from a principal component analysis), and canonical weights, which quantify the relative importance of each variable's contribution to each latent construct. We considered alternative analysis methods, such as multivariate multiple regression, but CCA will yield the richest information set and allow us to understand the dimensionality of the relationships between physical and cognitive aging, without defining variables as exposure or outcome. Using CCA will also reduce the likelihood of false discovery; alternative procedures would require running multiple models to investigate all outcomes of interest. We will define two variable sets using measures of physical aging and cognitive aging (see Variable Sets below). Data will be examined for normality, and standard descriptive statistics, including frequencies and measures of central tendency and dispersion where appropriate, will be used to describe the sample. We will examine bivariate relationships between demographic/clinical variables and physical and cognitive aging measures to further characterize the sample. Variables to be included in the CCA will be examined for meeting statistical assumptions, followed by generating canonical correlations for each canonical variate pair. Significantly correlated pairs will be retained and used to construct a series of correlation matrices, through which we will identify the canonical weights of individual variables and their correlation with each canonical variate and member variables. We will identify 1) the degree of shared variance between latent constructs of physical and cognitive aging using likelihood ratio tests (Wilks lambda) on each canonical variate, and 2) the individual variables responsible for the most shared variance using communality coefficients (h^2).

Variable Sets for CCA: CCA does not require variables to be defined as an exposure or outcome; instead variables are assigned to a conceptually meaningful group. For Aim 1, physical aging (variable set #1) is indexed by objective and perceived mobility, and cognitive aging (variable set #2) is indexed by depression, fatigue, and cognitive functioning. See Table 2 for list of variables and corresponding measures.

Confounders: CCA does not accommodate inclusion of potential confounding variables. As part of initial analyses to understand the sample, we will examine bivariate relationships between physical and cognitive aging measures and potential confounders (age, body mass index (BMI), time since diagnosis, cancer stage, and other treatments (e.g. surgery, radiation, chemotherapy)).

Power and Sample Size: With a sample size of 284 men and an alpha of 0.05, we will have 80% power to detect a correlation between canonical variates of physical aging and cognitive aging of r=0.17 (small-medium effect size; small r=.1, medium r=.25).

Aim 2: As in Aim 1, we will use canonical correlation analysis (CCA) to evaluate relationships between physical and cognitive aging measured at a single timepoint. For Aim 2, we will define two variable sets using measures of physical aging and cognitive aging (see Variable Sets below). Analyses will proceed as in Aim 1.

Variable Sets for CCA: For Aim 2, physical aging (variable set #1) is indexed by metrics of daily life mobility, and cognitive aging (variable set #2) is indexed by depression, fatigue, and cognitive functioning. See Table 3 above for list of variables and corresponding measures.

Power and Sample Size: With a sample size of 65 and an alpha of 0.05, we will have 80% power to detect a correlation between canonical variates of physical aging and cognitive aging of r=0.34 (medium effect size).

14.0 RECRUITMENT METHODS

We have planned for a 40-month enrollment period (see **Timeline**) to recruit 360 men into the proposed study (9 participants/month). This enrollment rate is similar to that in our previous

studies in prostate cancer survivors on ADT [38] and of women cancer survivors into a fall prevention study (N=466). Men will be enrolled into 8 waves of 45 men to maintain reasonable class sizes (15 men per class). Our primary recruitment strategy will be through the Oregon State Cancer Registry (OSCaR), which we have used for previous studies. Typically, 50%-80% of potential participants in our prior trials are respondents from OSCaR recruiting efforts. Current records indicate that there are 6112 living prostate cancer survivors who meet our age criteria in the Portland metro area. Based on recent estimates of ADT use, we expect 45% of this pool to be current or past ADT users and of this group we expect ~25% to be ineligible because they have no sign of frailty and/or have a cognitive limitation or medical contraindications to exercise yielding 2062 men. In our prior studies, ~20% of eligible survivors enroll in exercise trials so using this estimate we could expect to enroll up to 412 men, exceeding our target sample using the registry alone. Since prostate cancer disproportionately affects African American men, we also partner with the African American Health Coalition to recruit African American prostate cancer survivors into the trial. We will also recruit by clinician referral through OHSU Hospital (led by Co-I Hung) and OHSU Community Oncology clinics that serve outer Portland area. Physicians have referred up to 15% of enrollees in past exercise studies. We will also use direct community recruitment using newspaper ads, radio, web and presentations at cancer organizations and conferences, which have yielded ~15%-20% of participants in past trials. We may also receive patient information (e.g., name, phone number, e-mail address, mailing address, and minimal eligibility-related cancer history information) for recruitment purposes from various hospital systems such as Tuality Healthcare and Adventist Medical Center as well as from OHSU sources such as OCTRI's Cohort Discovery, Research Data Warehouse, and OHSU's medical records. After obtaining this demographic data, recruitment will occur via letters, e-mails, phone calls, or letters/announcements via MyChart.

This study will use Epic MyChart® to recruit potential participants. Researchers will work with ITG and/or OCTRI to identify potential participants based upon the above eligibility criteria. Researchers will create a Reporting Workbench query in epic based on inclusion and exclusion criteria. Potential participants will be sent a MyChart® recruitment message asking them to participate. There is no risk of duplicate invitations as it is based on MyChart® accounts combined with Epic records and no duplication is possible.

Ancillary study: In addition to the recruitment methods listed above, we will reach out to current and past study participants who have given their permission to be contacted about future study opportunities.

15.0 INFORMED CONSENT (REQUIRED, UNLESS A WAIVER OR ALTERATION IS APPROVED BY THE IRB)

Written informed consent will be obtained from all participants. A copy of the consent form and documentation of consent will be maintained in the participant's medical record as well as stored in a study file kept in a locked cabinet in the Knight Cancer Research Building (for paper documents only) or stored on an encrypted and password protected computer drive in the OHSU Knight Cancer Research Building (for electronic consents and scanned PDFs of paper consents). Electronic data, including the electronic consent, will also be stored in a web-accessible REDCap database housed on an OHSU secure server.

Interested and eligible participants will go to OHSU to meet with the study coordinator to sign a consent form. The study coordinator and PI will make themselves available throughout the consent process to answer any questions regarding the study. The study coordinator will ask

the participant to reflect back the details of the study to ensure the participant's understanding. The participant will also be given a copy of the signed consent form to take home and refer to whenever needed. Participants will be told that participation is voluntary and they may discontinue participation at any time and that participation will not affect their usual care.

Re-consent for modified procedures will be done over the phone or via teleconference. Study team members will inform the participants of the modified procedures and note their verbal agreement to continue on the study.

Individuals who have not previously consented will be screened by phone or teleconference using an IRB approved screening script. After initial screening, interested and eligible participants will consent by an electronic consent process setup through OCTRI's REDCap system (See 17.0 for a description of REDCap's Privacy, Confidentiality, and Data Security). A waiver of documentation of consent will be used to waive the need for a legally valid signature, however, an electronic signature and affirmation of consent will be collected in REDCap. Study staff will sign an attestation form in REDCap after the participant consents. Study staff will proceed with following the outline for remote testing procedures, as previously described in section 3.0 Study Design/Methodology.

16.0 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the Knight Cancer Institute and the IRB before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the IRB in writing within 5 working days after the implementation.

17.0 PRIVACY, CONFIDENTIALITY, AND DATA SECURITY

Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Paper files will be stored in locked filing cabinets in restricted access offices at OHSU Knight Cancer Research Building.

Electronic data will be stored on an encrypted and password protected computer drive in the OHSU Knight Cancer Research Building.

Electronic data will also be stored in a web-accessible REDCap database housed on an OHSU secure server. Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.

- Controlled User Access: REDCap is employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes “single click” ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

Access to data is restricted to study personnel and requires OHSU ID/password authentication.

Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code.

Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN)

The key associating the codes and the subjects personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

Data will be transferred in files using encryption.

Data released to other investigators will be labeled with only the code.

Data from this study will be banked in a repository for future use as part of this protocol. Access to data is restricted to study personnel.

18.0 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Reportable New Information (RNI) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site:

- Fatal and life-threatening events will be reported to OHSU IRB within 5 days of notification of the event. All other reportable events will be submitted to OHSU IRB no later than 5 working days of occurrence or notification of the event. Copies of the report documents will be kept in the study regulatory binder.
- Reportable events are submitted through OHSU eIRB and will be reviewed by OHSU Knight Cancer Institute DSMC and IRB.

19.0 OHSU KNIGHT CANCER INSTITUTE DATA AND SAFETY MONITORING PLAN

In addition to complete study and pharmacy files, complete records must be maintained on each patient enrolled on this protocol. OHSU Knight Clinical Research Quality and Administration (CRQA) shared resource is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, state laws, FDA regulations (where applicable), Department of Health & Human Services (DHHS) regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on Knight approved protocols according to the Data and Safety Monitoring Plan, policies and procedures. Locally initiated observational and low risk interventional studies may be audited by an OHSU Knight DSMC audit team any time after enrollment begins. The Quality Assurance audit process provides assurance that the reported data accurately reflects the data in the primary patient record and that regulatory requirements are met.

19.1 Monitoring Plan:

This study represents a moderate risk to study participants because it is a clinical trial involving human subjects. Though physical activity and exercise may be associated with adverse events (e.g. tiredness, muscle soreness, muscular injury, cardiac events, shortness of breath), most such events are associated with inappropriately vigorous exercise, which is not the objective of this study.[66] The study will be wholly overseen by the OHSU NCI-designated Comprehensive Cancer Institute for both safety and compliance to institutional and NCI policies. The PI is responsible for evaluating each adverse event as it occurs and for notifying the OHSU IRB of the occurrence of an adverse event according to IRB protocols. An interim safety review will occur early in the intervention period to determine potential safety concerns before the total sample has been accrued. The interim safety review will be overseen by OHSU Knight Data Safety and Monitoring Committee (DSMC, see details below) and will occur after the first 45 enrolled men (~1/8th of total sample) have completed 3 months of exercise training to assess early for program safety.

Adverse events related or possibly related to exercise sessions (i.e., group exercise classes, prescribed home program exercise, and physical performance measurement appointments) will be graded according to their significance for severe consequences, such as injury or death, using the following grades determined by the OHSU IRB.

Examples of serious adverse events (life-threatening or disabling and requiring medical attention). Serious adverse events that may occur during exercise in this study include death and cardiovascular events, though these are extremely rare in the absence of significant cardiac pathology.

Examples of moderate adverse events (resolve with treatment). Moderate adverse events that may occur during exercise include symptoms, such as shortness of breath and orthostatic intolerance.

Examples of mild adverse events (do not require treatment). Reports of side effects, such as muscle soreness, moderate tiredness while exercising, and similar discomforts are mild adverse events.

Examples of unexpected adverse events that do not include physical harm. Adverse events can also include breaches of confidentiality, emotional harms, or complaints about study procedures or conduct of investigators.

In this study we do not anticipate moderate or serious adverse events. Only moderate and serious adverse events that are related or possibly related to exercise sessions (i.e., group exercise classes, prescribed home program exercise, and physical performance measurement appointments) will be reported on our Adverse Events Log.

A survey (Adverse Events Survey) was created by the study team to be adminstered monthly during the participants' year long participation in the study. Adverse events reported through this survey may be followed-up by study staff with a phone call, e-mail, or in person in class during the intervention period, when participants self-report that their reporting condition is due to a study-related exercise activity or if more information is needed to determine reportability. Participants will also have the opportunity to report adverse events during exercise class or at physcial performance measurement appointments.

19.2. Plan for Reporting Adverse Events

Serious adverse events will be reported immediately to the Principal Investigator (PI), who will immediately notify all other investigators. The PI will file a full written report to the OHSU Institutional Review Board (IRB) within 24 hours of notification of the serious event, as required by the OHSU IRB. Specifically, the following will be reported, in writing: 1) all deaths in study participants, during the intervention period, regardless of cause, 2) all serious adverse events associated with the study procedures

Moderate adverse events will be tabulated by the PI, who will notify members of the research team if trends are identified. If trends are noted, preventive measures will be implemented, such as providing education of participants in the study to emphasize prevention of the adverse event. Moderate adverse events will be included in annual reports to the OHSU IRB.

Mild adverse events will not be formally logged but, participants will receive advice on avoiding such events.

Unexpected adverse events that do not include physical harm, usually having to do with study procedures, will be reported within 10 days to OHSU IRB, using a written report form.

Adverse events will be reported to NIH according to NIH protocols.

19.3. Guidelines to Stop the Study

Cardiac events or deaths are very rare in persons engaging in low or moderate intensity exercise, though it is possible that a person with previously undisclosed cardiovascular disease may experience a cardiac event or death during exercise. Regardless of cause, we are required to notify the OHSU IRB within 24 hours if a participant dies during this study. We will stop the study if the IRB instructs us to do so.

19.4 Data Safety and Monitoring Committee

The OHSU Knight Cancer Institute Data and Safety Monitoring Committee (DSMC) is responsible for overall coordination of all aspects of the DSMP. The internal audit team conducts quality assurance audits on all open clinical trials that are not monitored by another source. The DSMC meets once each month to review the audit team's progress and findings and to review significant adverse events (SAE) and/or unanticipated problem (UP) reports, and Interim Analysis reports. The DSMC also reviews a full report of study activity for all local, active clinical trials at the time of continuing review submission including:

- protocol amendments, revisions, consent form revisions
- interim analysis results
- protocol violations
- total number of patients enrolled on-study as compared to expected numbers
- dates of patient enrollments
- vital and study (on or off-study) status of each patient
- all Unanticipated Problems submitted (including dates, description and relationship)

Members receive this information approximately one week prior to Committee meetings, to allow for preliminary study and review. The Committee will vote to approve, conditionally approve (enrollment may continue after satisfactory response by the principal investigator to DSMC is

received), suspend or close each protocol reviewed. The Committee decision will be documented in monthly meeting minutes. Principal investigators may appeal the decision to the Director of the Cancer Institute.

The DSMC oversees the process of serious adverse event reporting to assure that reporting requirements are met. The DSMC may require amendments, suspend or terminate any clinical trial that falls within its jurisdiction. The DSMC has the authority to report directly to the OHSU IRB. The DSMC communicates with and provides semi-annual summary reports to the Knight Cancer Regulatory Committee.

The DSMC is made up of the following representatives: physician members of OHSU Knight Cancer Institute, administrators of Clinical Research Management (CRM), biostatistician, research pharmacist, research nurses, and study coordinators. A term of membership is 5 years. In the event that a Committee member is key personnel (principal investigator, co-investigator, biostatistician, study coordinator, study investigational pharmacist, study nurse) for a study under review, or has any other conflict of interest (including substantial financial interest in the study sponsor agency), that member must abstain from Committee review and discussion and must leave the room prior to final decisions on the study. In the event that the Chair is the principal investigator for the study, the Co-Chair of the Committee will oversee the Committee deliberations and final decisions. The Knight DSM Committee includes multiple MD representatives as well as an alternate biostatistician for cases in which our primary biostatistician has a conflict of interest.

20.0 INCLUSION OF WOMEN, MINORITIES AND CHILDREN

Women will be excluded from this study because this study is in prostate cancer survivors only. No men from racial or ethnic groups will be excluded if they meet the criteria for enrollment in the study.

The projected gender, racial and ethnic composition of the study will include a higher proportion of African American men than state demographics because the prostate cancer disproportionately affects African Americans.

Table 1: Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6

Ethnic Category	Sex/Gender		
	Females	Males	Total
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Table 2: Projected Accrual for the Present Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino		42		42
Not Hispanic or Latino		318		318
Unknown				
Ethnic Category: Total of all subjects*		360		360
Racial Category				
American Indian or Alaskan Native		5		5
Asian		13		13
Black or African American		7		7
Native Hawaiian or other Pacific Islander		1		1
White		301		301
More than one race		14		14
Unknown		19		19
Racial Category: Total of all subjects*		360		360*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Ancillary study:

Table 3: Projected Accrual for the Ancillary Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino		15		15

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Not Hispanic or Latino		115		115
Unknown				
Ethnic Category: Total of all subjects		130		130
Racial Category				
American Indian or Alaskan Native		2		2
Asian		5		5
Black or African American		2		2
Native Hawaiian or other Pacific Islander		0		0
White		109		109
More than one race		5		5
Unknown		7		7
Racial Category: Total of all subjects		130		130

Source: Adapted from U.S. Census Bureau, 2010

21.0 INCLUSION OF CHILDREN

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children for the following reason:

Prostate cancer is exceptionally rare under the age of 21. When diagnosed in children it is considered an anomaly and a much different disease. Thus, children will be excluded from this study.

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